ALEVE® (NAPROXEN SODIUM)
&
NAPROSYN® (NAPROXEN)
ANAPROX® (NAPROXEN SODIUM)

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Briefing Document
for
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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Abbreviation	Definition
ADAPT	Alzheimer's Disease Anti-inflammatory Prevention Trial
AMI	Acute myocardial infarction
APTC	Antiplatelet Trialists' Collaboration
ASA	Aspirin
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
COX	Cyclooxygenase
COX-1	Cyclooxygenase isozyme-1
COX-2	Cyclooxygenase isozyme-2
CV	Cardiovascular
CVA	Cerebrovascular accident
EMA	European Medicines Agency
FDA	US Food and Drug Administration
HR	Hazard Ratio
MI	Myocardial infarction
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds Ratio
OTC	Over-the-counter
PGI_2	Prostacyclin
PGHS	Prostaglandin G/H synthase
PY	Patient-years
RR	Relative Risk
TARGET	Therapeutic Arthritis Research and Gastrointestinal Event
TXA2	Thromboxane A2
TXB2	Thromboxane B2

1. Executive Summary

The body of evidence continues to show little to no increase in cardiovascular (CV) risk with naproxen/naproxen sodium[a] and supports its favorable CV safety profile among selective and non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) today, as it did in 2005, when the Advisory Committee and the Food and Drug Administration (FDA) previously reviewed the CV safety of NSAIDs.

FDA is assembling an Advisory Committee to review the cumulative data published since 2005 to further review the appropriateness of the current information about NSAIDs and CV thrombotic risk that is currently described in NSAID class labeling.

Based on the 2005 FDA-Advisory Committee conclusions and the data on CV safety of selective and non-selective NSAIDs available at that time, we understand the rationale behind the use of class labeling for non-aspirin NSAIDs. Nevertheless, guidelines, publications and possibly the label should clearly and accurately communicate the conclusions from the vast body of evidence that continues to demonstrate the low CV risk for naproxen, particularly for Aleve®, in its over-the-counter (OTC) setting.

1.1 Background

Naproxen, an NSAID approved in 1976, is currently available in the United States (US) for both prescription use marketed by Genetech, a member of the Roche group and OTC use marketed by Bayer Healthcare LLC, Consumer Care. In addition, multiple generic versions of naproxen are currently available. Naproxen sodium is marketed as a nonprescription product by Bayer under the brand names Aleve® and Midol Extended Relief®. Roche markets the prescription brands Naprosyn® (naproxen) and Anaprox® (naproxen sodium).

Bayer also markets naproxen sodium in over 50 countries, including Australia and numerous European, South American, African, Asian and Caribbean countries. The earliest approval outside the US was in 1981. In most countries, the approved non-prescription dosing regimen for the temporary relief of aches and pains and the reduction of fever is 550 mg or 660 mg daily in adults and children 12 years of age and older. In general, the labeling for the global products mimics that of the United States with variations generally attributable to the mandates of the local Health Authority.

After a US FDA review in 2005, the label of all prescription non-aspirin NSAIDs was updated to include a warning highlighting the potential for increased risk of cardiovascular (CV) events. OTC non-aspirin NSAID labeling was revised to include a statement in the Warnings section.[b] In addition, both the prescription and OTC labeling were revised to include a warning of gastrointestinal (GI) bleeding and a warning regarding allergic skin reactions associated with their use. The FDA review was undertaken after the withdrawal of rofecoxib from the market based on an increased risk for acute myocardial infarction (AMI) and stroke in the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial. As of 2005, little to no evidence of an

[a] Currently approved OTC formulations only include the naproxen sodium salt. For purposes of this review, these formulations will be referred to as "naproxen" unless additional clarity is needed.

[b] "When using this product…the risk of heart attack or stroke may increase if you use more than directed or for longer than directed."

increased CV risk was detected with naproxen. Specifically, in its 2005 Advisory Committee briefing document, Bayer and Roche submitted extensive evidence supporting the CV safety of naproxen. This included:

- A review of observational studies of naproxen and cardiovascular outcomes covering the period of 1987 to date and involving over 80,000 patients exposed to naproxen that showed no increased cardiovascular risk with naproxen; and which included several studies that suggested that naproxen may have an aspirin-like cardioprotective effect.[c]
- A review of Roche postmarketing surveillance data that showed no signal for AMI/MI or cerebrovascular accident with exposures to prescription naproxen of 113,188,125 patients from June 1, 1995 until December 21, 2004.
- A review of the Bayer OTC postmarketing surveillance data from April 2001 until December 23, 2004 that did not identify a signal for AMI/MI or cerebrovascular accident with an estimate of 550,000,000 courses of therapy and was consistent with the Roche data.
- Clinical studies in the prescription and OTC naproxen New Drug Applications that showed no evidence of an increased risk of cardiovascular events (AMI/MI).
- Postmarketing clinical studies, with the exception of the ADAPT study, which showed no evidence of an increased risk of cardiovascular events with naproxen.
- Clinical pharmacology data, which showed that naproxen would not be expected to have an adverse effect on cardiovascular risk from its ability to inhibit platelet aggregation through its effects on COX-1.

As of 2005, the conclusion from Bayer and Roche was that the vast majority of data showed little to no relationship between an increased risk of MI and cerebrovascular accidents and the use of naproxen.

In February 2014, FDA Advisory Committees will review published literature on the CV safety of non-aspirin NSAIDs published since 2005, specifically focused on the risk of CV thromboembolic events.

In this document, Bayer and Roche provide a comprehensive evaluation of data since 2005, which continue to support the conclusion that naproxen at prescription and OTC doses have a low CV risk profile. Also, in line with FDAs findings in 2005, short-term use of low doses of non-prescription NSAIDs is not associated with an increased risk of CV events.

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[c] Aspirin's cardioprotective effects involve the prevention of cardiovascular (CV) thrombotic events in patients with or those at risk for cardiovascular disease (CVD). Specifically, the CV prevention indications for aspirin are, "To reduce the risk of death and nonfatal stroke with previous ischemic stroke or transient ischemia of the brain. To reduce risk of vascular mortality with suspected acute myocardial infarction (MI). To reduce risk of death and nonfatal MI with previous MI or unstable angina. To reduce risk of MI and sudden death in chronic stable angina pectoris. For patients who have undergone revascularization procedures with a preexisting condition for which aspirin is indicated."

1.2 Cardiovascular Safety Results

The main results from this updated review of published data on the CV safety of naproxen since 2005 are as follows:

i. While discussed at the 2005 FDA Advisory Committee, two clinical studies, ADAPT (Alzheimer's Disease Anti-inflammatory Prevention Trial) and TARGET (Therapeutic Arthritis Research and Gastrointestinal Event) naproxen substudy, were published after 2005. A review of these two postmarketing clinical studies showed no evidence of a statistically significant increased risk of MI, stroke or congestive heart failure (CHF) in the naproxen treatment groups. The only statistically significant result – reported in a substudy analysis from the TARGET trial – showed that naproxen had a lower risk of composite CV outcome compared to lumiracoxib in osteoarthritis patients with a high baseline CV risk who were not taking low-dose aspirin.

ii. A review of 35 observational studies showed little to no evidence for increased risk of MI, stroke, or CHF in patients exposed to naproxen. Of the 35 studies that reported on prescription doses of naproxen, only a few studies reported statistically significant increases in the risk of thromboembolic events (4 for MI events and 4 for ischemic stroke events). Five out of 6 studies that included data on OTC doses of naproxen use showed no statistically significant increased risk for thromboembolic events. The results should be interpreted in context of the study population, study design, and other limitations common to retrospective and observational studies. Only two observational studies reported CHF safety data during any dose of naproxen use, neither of which showed a statistically significant increased risk.

iii. A review of 6 meta-analyses of randomized controlled trials (RCTs) showed no statistically significant evidence for an increased risk of MI or stroke in patients exposed to OTC or prescription doses of naproxen. A statistically significant increase in hospitalizations due to CHF during prescription naproxen use was reported in a single meta-analysis, but the risk of CHF-related hospitalization was not different among the NSAIDs examined in the study.

iv. A review of 4 meta-analyses of observational studies also supported the finding that there is no evidence of statistically significant increased risk of an MI or stroke during OTC or prescription use of naproxen. A single meta-analysis that looked at the risk of a composite of MI, stroke, and CV death, did report a statistically significant increase in CV risk during use of prescription dose naproxen; however, the measured CV outcome included non-thromboembolic events as part of CV death.

v. A review of both the Roche prescription naproxen and Bayer OTC pharmacovigilance worldwide safety databases did not indicate a signal for either MI or cerebrovascular accidents.

vi. Since 2005, evidence from clinical pharmacology experiments indicates that naproxen, given in divided daily doses, produces > 95% platelet inhibition, similar to the antiplatelet effect of aspirin. Selected data suggest some interaction between naproxen and the antiplatelet activity of aspirin, if dosed prior to or concomitantly with aspirin. However, there is no evidence that occasional use of OTC doses of naproxen given with aspirin interferes with aspirin's cardioprotective effect.

vii. One consistent finding with multiple statistically significant outcomes was the reduced risk of thromboembolic events during naproxen use in comparison to several individual cyclooxygenase isozyme-2 (COX-2) specific inhibitors and non-naproxen NSAIDs. Specifically, large meta-analyses of RCTs in patients exposed to any dose of naproxen compared to COX-2 selective inhibitors and non-selective NSAIDs showed a general reduced risk for MI (statistically significant lower risk was found in some stroke and composite CV outcomes) with naproxen.

1.3 Conclusions

The evidence since 2005 shows little to no association of an increased thromboembolic risk with naproxen. The body of evidence supports the CV safety of naproxen at both OTC doses (≤600-660 mg/day) and prescription doses (>600-660 mg/day). Some evidence even suggests that naproxen may decrease the risk of MI and composite of thromboembolic events. Furthermore, the data consistently demonstrate that naproxen has a lower overall CV risk than other selective and non-selective non-aspirin NSAIDs.

2. Introduction

Naproxen, an NSAID, is currently available in the US for both prescription and OTC use. It was approved for prescription use in the US in 1976 and was made available for OTC use as Aleve® (naproxen sodium 220 mg) in the US in 1994. Naproxen, as well as other NSAIDs, plays an important role in the chronic and acute treatment of pain and inflammation. The benefit/risk profile has been well established over the past 37 years.

After an FDA review in 2005, the labeling of all prescription and OTC non-aspirin NSAIDs was updated to include warnings highlighting the potential for increased risk of CV events.[d]

In February 2014, FDA Advisory Committees will review additional published evidence on the CV safety of non-aspirin NSAIDs since 2005, specifically focused on the risk of thromboembolic events.

Bayer Healthcare Consumer Care and Roche have independently routinely monitored the potential increased risk for CV events associated to the use of NSAIDs. In preparation for the FDA Advisory Committee meeting, Bayer and Roche have jointly undertaken an updated evaluation and cumulative review of the published safety data available for naproxen since 2005 to assess the risk of CV thromboembolic events.

3. Background on Naproxen

3.1 Naproxen Indications and Labeling

Naproxen is currently available in the US by prescription and OTC. It was originally developed by Syntex and was acquired by Roche in 1994. **Table 3-1** provides the regulatory history of naproxen.

[d] The FDA Postmarketing Drug Safety Information was published online on April 7, 2005, available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm

Table 3-1: Regulatory Chronology for Naproxen in the US

1976	Original prescription approval in the US for the relief of signs and symptoms of rheumatoid arthritis
1980	Additional prescription indications: osteoarthritis, analgesic use and dysmenorrhea
1983	Additional prescription indications: ankylosing spondylitis, tendonitis, bursitis and acute gout
1986	Additional prescription indication: juvenile arthritis
1994	Approval for OTC use (Aleve®)
2005	As part of a NSAID class-wide request by FDA: Prescription label -Boxed warnings highlighting the potential for increased risk of CV events and serious, and potentially life-threatening GI bleeding events were added
	OTC Drug Facts -Warnings about potential CV and GI risks were added -A warning about potential allergic skin reactions -Instructions about which patients should seek the advice of a physician before use -Stronger reminders about limiting the dose and duration of treatment in accordance with package instructions, unless otherwise advised by a physician.

The current indications for prescription naproxen[e] in the US include relief of the signs and symptoms of rheumatoid arthritis (RA), osteoarthritis (OA), ankylosing spondylitis (AS) and juvenile arthritis (JA). All forms, except EC-Naprosyn (enteric-coated naproxen), also carry indications for relief of the signs and symptoms of acute gout, and for the management of pain, tendonitis, bursitis and of primary dysmenorrhea.

OTC naproxen sodium (Aleve®) was approved in 1994 for short-term episodic use with labeling that reflects its well-established benefit/risk profile. The approval of naproxen for OTC administration was supported by more than 18 years of experience with prescription strength naproxen and naproxen sodium. OTC naproxen sodium is indicated for temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, arthritis, menstrual cramps, and for the reduction of fever in adults and children 12 years of age or older. In the United States the OTC dose of naproxen sodium is 220-440 mg as a single dose with a maximum total daily dose of 660 mg. The dosing interval for OTC naproxen sodium is every 8-12 hours while symptoms persist.

Following the 2005 Advisory Committee meeting, FDA requested that manufacturers of non-aspirin prescription and OTC NSAIDs revise their labels to include a warning highlighting the potential for increased risk of CV events. The current OTC label for naproxen is provided in **Appendix 1** and the version prior to the label change in 2005 is provided in **Appendix 2** for reference.

[e] Dosage for Naprosyn and Anaprox are as follows: *Adults:* RA/OA/AS: (Naprosyn) 250mg, 375mg, or 500mg bid. (Anaprox) 275mg bid. Titrate: Adjust dose/frequency up or down depending on clinical response; may increase to 1500mg/day for ≤6 months if patient can tolerate lower doses well. Pain/Dysmenorrhea/Tendonitis/Bursitis: (Anaprox) Initial: 550mg, then 550mg q12h or 275mg q6-8h as required. Max: 1375mg/day initially, 1100mg/day thereafter. Acute Gout: (Naprosyn) Initial: 750mg, then 250mg q8h until attack subsides. (Anaprox) Initial: 825mg, then 275mg q8h until attack subsides. *Pediatrics*: ≥2 Yrs: JA: (Sus) Usual: 5mg/kg bid.

FDA is assembling an Advisory Committee to review the data published since 2005 to further understand the relationship between NSAIDs and CV thrombotic risk that is currently described in NSAID class labeling safety of NSAIDs.

Based on the 2005 FDA Advisory Committee conclusions and the data on CV safety of selective and non-selective NSAIDs available at that time, we understand the rationale behind the use of non-aspirin NSAID class labeling. Nevertheless, guidelines, publications and possibly the label should communicate the vast body of evidence demonstrating the low CV risk for naproxen, particularly for Aleve® in its OTC setting.

3.2 NSAID Clinical Pharmacology

NSAIDs are a heterogeneous set of compounds that have important anti-inflammatory, analgesic, and antipyretic properties. NSAIDs consist of several major chemical classes, e.g., salicyclic acid derivatives, indole and indene acetic acids, heteroaryl acetic acids, arylpropionic acids, anthranilic acids, enolic acids and alkanones.

The major mechanism of action of NSAIDs is based on the inhibition of prostaglandin G/H synthase (PGHS), also named COX, an enzyme that plays a key role in different physiological functions, but also in the process of inflammation. Each of the compounds inhibits COX by different binding mechanisms.

NSAIDs are often categorized as non-selective or selective NSAIDs based on COX inhibition. The non-selective NSAIDs inhibit both COX-1 and COX-2 enzymes; naproxen, aspirin, diclofenac, ibuprofen, indomethacin, ketoprofen, and piroxicam are some examples of non-selective NSAIDs. The relative specificity for COX-1 varies among non-selective NSAIDs. The selective COX-2 inhibitors (also referred to as coxibs), such as celecoxib, lumiracoxib, celecoxib, rofecoxib, and etoricoxib, specifically inhibit the COX-2 enzyme. Since COX-1 activity promotes platelet aggregation, selective COX-2 inhibitors do not have antiplatelet effects associated with non-selective NSAIDs.

The majority of the NSAIDs, including naproxen, act as reversible, competitive inhibitors of COX. As the inhibition is reversible, the duration of action for the non-selective NSAIDs is primarily related to their pharmacokinetic clearance.[1] Aspirin irreversibly inhibits COX-1.

3.3 Pharmacological Properties of Naproxen

Naproxen possesses the three properties now universally accepted as being characteristics of NSAIDs; anti-inflammatory, analgesic and antipyretic properties.[2] Naproxen is highly bioavailable orally (95%). The plasma levels are directly proportional to the drug dosage[3]; however, there is a decrease in the proportion of plasma-binding for naproxen/naproxen sodium at doses >500 mg/day due to saturation.[3] Peak concentrations occur within 2 to 4 hours and more rapidly with naproxen sodium.[4] The half-life of naproxen ranges from 12 to 17 hours, and the metabolites have a shorter half-life of <12 hours.

Naproxen is a member of the chemical class of propionic acid derivatives. This widely used class also includes ibuprofen, fenoprofen, ketoprofen, flurbiprofen, and oxaprozin. Treatment with these agents results in reductions in pain, joint swelling, and duration of morning stiffness.[5] Treatment also results in improvements in strength and mobility. The major differences between the members of this chemical class are potency and pharmacokinetics.

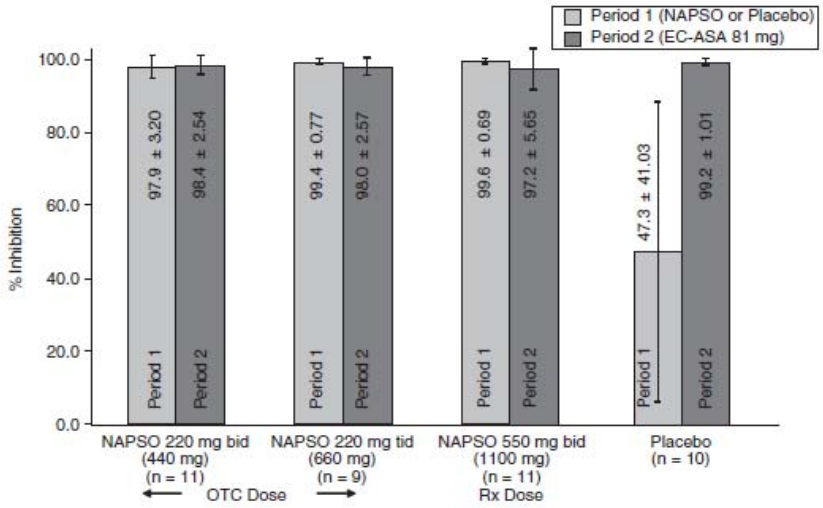
The major pharmacological difference between naproxen, a non-selective COX inhibitor, and selective COX-2 inhibitors is a direct consequence of the capacity to inhibit one or both COX isozymes. Naproxen inhibits both the formation of 1) COX-1 dependent thromboxane synthase A2 (TXA2) which reduces platelet aggregation, and 2) the COX-2 dependent prostacyclin (PGI_2) which is an important vasodilatory mediator. In contrast, selective COX-2 inhibitors decrease the production of PGI_2, but have no effect on TXA2 production.[1]

3.4 Naproxen inhibits platelet aggregation

Naproxen is a dual COX-1/COX-2 inhibitor. Naproxen is known to inhibit platelet aggregation through its effects on COX-1 and thus, could potentially decrease the risk of cardiovascular events.

Schiff *et al.* (2009) conducted an outpatient, open-label, randomized, placebo controlled, two-way crossover, phase I, single-center study.[6] Subjects were randomized in a 1:1:1:1 ratio to receive one of three regimens of naproxen sodium (NAPSO)(NAPSO 220 mg twice daily, NAPSO 220 mg three times daily, NAPSO 550 mg twice daily) or placebo (twice daily) for 7 days (period 1). After 7 days of treatment with NAPSO, mean inhibition of serum thromboxane B2 (TXB2), an inactive metabolite of TXA2 (measured 24 h following the day 7 morning dose) was >95% in all evaluable NAPSO-treated subjects and most patients exceeded 95% inhibition (**Figure 3-1**). The mean (SD) inhibition of serum TXB2 was 97.9% (3.20) for NAPSO 220 mg twice daily (range 90.5–100%), 99.4% (0.77) for NAPSO 220 mg three times daily (range 97.6–100%), and 99.6% (0.69) for NAPSO 550 mg twice daily (range 97.6–100%).

Figure 3-1: Mean percent inhibition of serum thromboxane B2 (TXB2) (day 7)



Source: Obtained from *Schiff et al., 2009*[6]

Capone *et al.* (2007) reported rapid and relatively complete inhibition of TXB2 (**Table 3-2**) with naproxen.[7] For 220 mg, 95% inhibition was reported at 2 hours post dose with modest recovery of TXB2 reported at 5, 8, and 12 hours post dose. At 24 hours post dose, TXB2 inhibition was reported to be 69%. At a dose of 440 mg significant TXB2 inhibition (greater than 90%) began

at 2 hours post dose and was sustained for at least 12 hours post dose. At 24 hours post-TXB2 inhibition was reported to be 85%.

Table 3-2: Thromboxane inhibition at time points following the final dose after 6 days of dosing with naproxen sodium 220 mg and 440 mg twice daily. (Capone *et al.*, 2007)

Time	% Thromboxane Inhibition ± SD	
	Naproxen sodium 220 mg BID (n=6)	Naproxen sodium 440 mg BID (n=6)
2 h	95.9 ± 5.1	99.2 ± 0.4
5 h	90.8 ± 8.6	98.3 ± 0.5
8 h	88.9 ± 10	96.7 ± 1
12 h	86.6 ± 7.1	92.9 ± 3.1
24 h	69.1 ± 19.9	85.3 ± 5.1

SD= standard deviation, BID=twice daily
Source: *Capone et al., 2007*[7]

The experiments outlined above indicate that naproxen, given in divided daily doses, produces > 95% thromboxane B2 inhibition, similar to aspirin.

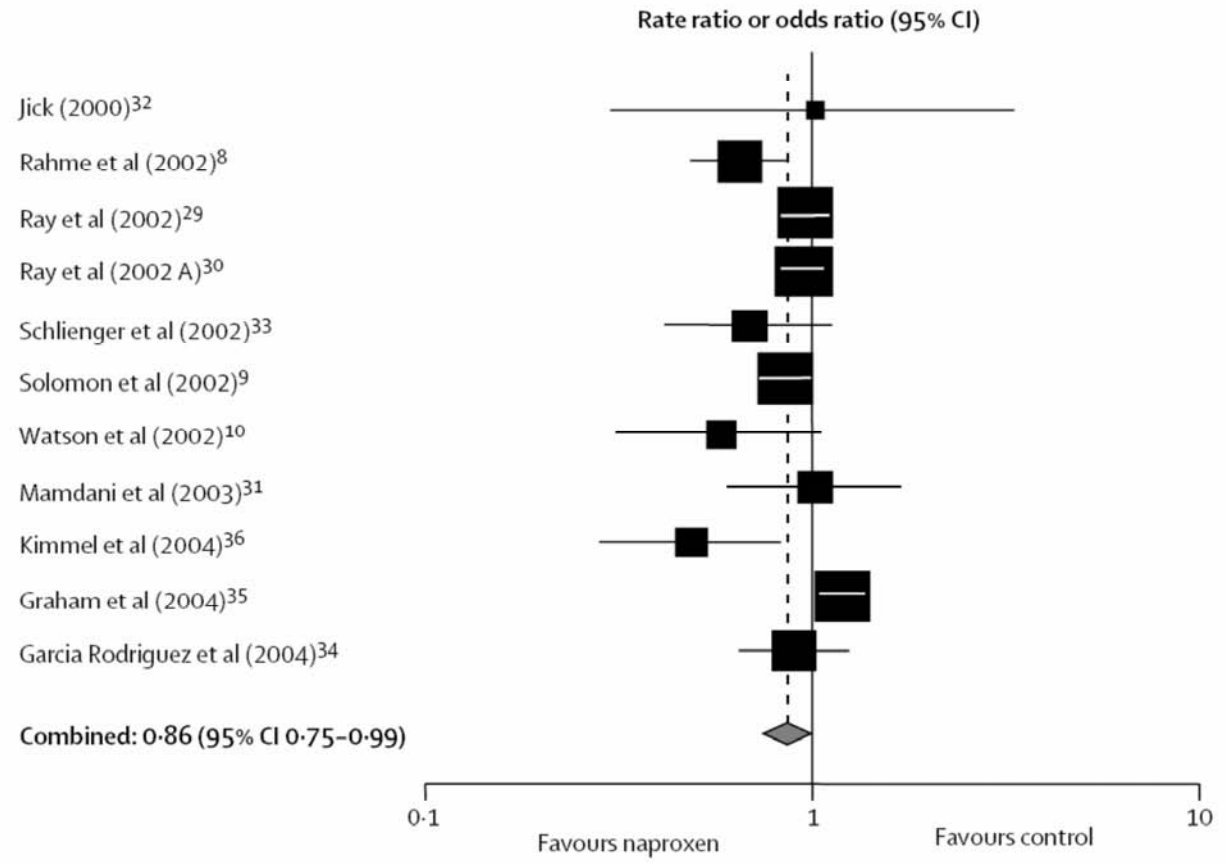
3.5 2005 US FDA Advisory Committee Meeting

3.5.1 Cardiovascular Safety Profile of Naproxen

The Roche/Bayer briefing book and presentation at the 2005 Advisory Committee Meeting discussed clinical study data that did not indicate any evidence of a safety signal for cardiovascular (AMI/MI) or cerebrovascular events.

A review of meta-analysis of observational studies up to 2005 indicated no evidence of an association between increased cardiovascular risk and the use of naproxen (**Figure 3-2**).[8] It should be noted that the duration of naproxen use was rarely ascertained in published observational studies.

Figure 3-2: Meta-analysis of Observational Studies of Naproxen and Risk of MI



Source: *Juni et al., 2004* [8]

Based on the 2005 FDA Advisory Committee conclusions and the data on CV safety of selective and non-selective NSAIDs available at the time, we understand the rationale behind the use of non-aspirin NSAID class labeling. Nevertheless, guidelines, publications and possibly the label should communicate the vast body of evidence demonstrating the low CV risk for naproxen, particularly for Aleve® in its OTC setting. The FDA remarked in its 2005 review that OTC doses of non-aspirin NSAID products such as naproxen were generally well below the daily prescription doses.[9] The duration of treatment in the absence of physician instructions should be limited to 10 days. The FDA also noted the difficulty in generalizing evidence from controlled clinical trials of prescription products to low-dose, short-term use of non-prescription products since factors such as the indications for use and patient populations are different. However, they stated that any risk was expected to be minimal. While these studies were primarily designed to evaluate effectiveness, FDA stated that the absence of a signal of increased CV risk provided some reassurance of the safety of short-term use.[9]

4. 2012 Review of Cardiovascular Safety of NSAIDs by the European Medicines Agency (EMA)

In 2012, the European Medicines Agency finalized a review of recently published information on the cardiovascular safety of NSAIDs.[10] The Agency's Committee for Medicinal Products for Human Use (CHMP) assessed available published data sources, including meta-analyses of clinical trials and observational studies, and the results of a European Union-funded independent research project, the 'Safety of non-steroidal anti-inflammatory drugs' (SOS) project. The Agency confirmed findings from previous reviews, conducted in 2005 and 2006. Regarding naproxen, CHMP concluded that the CV risk findings remain unchanged from the 2006 report. They remarked that naproxen is associated with a lower risk for CV events than selective COX-2 inhibitors and other non-selective COX-1/COX-2 inhibitors.

CHMP also recognized the difficulty in extrapolating the evidence from trials with prescription dose to OTC, short-term use in different patient populations. However, it was their opinion that, for short-term OTC use, non-selective NSAIDs are safe and effective and infrequently associated with clinically significant side effects.

5. Review of Postmarketing Studies Reporting Cardiovascular Safety Data: 2006-2013

5.1 Background

Although individually we continually monitor new information regarding naproxen, in preparation for the February 2014 US FDA Advisory Committee meeting, Bayer and Roche have undertaken a joint review of published literature since 2005. The studies reviewed were obtained from a list of bibliographic references that was provided by FDA as well as from additional PubMed/MEDLINE searches conducted by the companies. The identified literature was reviewed and the inclusion and exclusion criteria are listed below.

A published study was included in this review if it met each of the following:

- Primary reference (i.e., publications as a direct result of original research, authored by the study investigators)
- Included and reported on a population exposed to naproxen
- Reported event rates or risk ratios specific to the naproxen-exposed patients
    - With 95% confidence intervals (CI) and/or p-values
    - Allowed statistical comparisons between naproxen users and a comparators group
- Any one or more measured study outcomes of interest
    - Thromboembolic events such as myocardial infarction (MI), acute MI (AMI), and ischemic stroke.[f]

[f] Some studies reported on events related to "all stroke," which includes ischemic as well as hemorrhagic strokes. This review summarized the risk of "all stroke" only when the rates for ischemic stroke were not available in a study. Additionally, some studies have included deep vein thrombosis, pulmonary embolism, and/or systemic thrombosis events as part of thromboembolic events.

- Composite outcomes containing one or more thromboembolic events. For example, Antiplatelet Trialists' Collaboration (APTC) definition of CV event (nonfatal MI, nonfatal stroke, and CV death). Another example is major vascular events, when it included MI and/or stroke.
- Congestive heart failure (CHF), which refers to a syndrome that includes conditions that impair cardiac output, e.g., cardiopulmonary disease. Only studies that referred to the outcome as 'congestive heart failure'/'CHF' or 'heart failure'/'HF' were included.

Published study was excluded if it met any of the following:

- Not in English
- Only reports naproxen exposure within a group of other NSAIDs
- Only reports all-cause mortality
- Only reports CV death, where the composite definition was not supplied

It is important to note that the definition for thromboembolic event or CHF may not be homogenous across studies. Where possible, the specific definition has been provided in summary tables in this document (Tables 5-1 through 5-7).

For studies examining the interaction of NSAIDs with aspirin, review of a study necessitated that both a naproxen + aspirin cohort and an aspirin alone cohort (reference group) were included.

5.2 Thromboembolic Events

5.2.1 Postmarketing Randomized Controlled Trials (RCTs)

There were two randomized controlled trials (RCTs) that have been published in which risk (hazard rates) (**Table 5-1**) of thromboembolic events during exposure to naproxen versus a placebo or comparator NSAID were examined.

5.2.1.1 ADAPT (2006)

The ADAPT Steering Committee suspended the ADAPT trial in December 2004 after increased cardiovascular risks with celecoxib were reported from the National Cancer Institute-sponsored Adenoma Prevention with Celecoxib (APC) trial. Despite limitations of the study, the post-hoc analysis showed no significant increased risk of cardiovascular events associated with naproxen.

In the ADAPT study, patients with a family history of Alzheimer's dementia were randomized to celecoxib (200 mg twice daily), or active comparator naproxen sodium (220 mg twice daily), or placebo.[11] Patients were followed for 1-46 months (median follow up times: naproxen 23.5 months and placebo 22.1 months), and patient-reported occurrence of CV death, MI, stroke, CHF, or TIA were recorded. The study yielded a non-significant risk of MI (Hazard Ratio (HR) 1.49, 95% CI: 0.69-3.22, p=0.31) and stroke (HR 2.13, 95% CI: 0.81-5.60, p=0.12) for patients using naproxen versus those on placebo. Major limitations of the ADAPT study are that it was not powered to evaluate MI or stroke outcomes, had a small number of events, and the patient-reported CV events were not clinically adjudicated, which places the accuracy of the incident events into question. Another major limitation is in extrapolating the results of the ADAPT study to the general population; the ADAPT study population was primarily elderly patients likely to have different risk factors.

5.2.1.2 TARGET Naproxen Substudy (2007)

The TARGET naproxen substudy showed that naproxen had a lower rate of cardiovascular events than lumiracoxib.

The TARGET study evaluated the safety of lumiracoxib (400 mg once daily) versus high-dose naproxen (500 mg twice daily) or lumiracoxib (400 mg once daily) versus ibuprofen (800 mg three times daily) for 52 weeks in patients with osteoarthritis.[12] In addition to a gastrointestinal endpoint, the study was designed with another primary composite endpoint of MI, stroke and CV death. In a post-hoc analysis, the naproxen substudy evaluated risk of the composite CV event based on the patients' baseline CV risk and on use of low-dose aspirin.[13] When users of low-dose aspirin and aspirin nonusers were combined, naproxen had a lower rate of CV events than lumiracoxib in both the low CV risk [estimated Relative Risk (RR) 0.63, 95% CI: 0.26-1.51] and high CV risk (estimated RR 0.70, 95% CI: 0.39-1.26) groups. The Cox proportional hazards model also yielded lower risk estimates for naproxen as compared to lumiracoxib for both the low CV risk (HR 0.88, 95% CI: 0.43-1.78, p=0.417) and high CV risk groups (no events in the naproxen group, p=0.027) of aspirin nonusers. In contrast to the ADAPT study, the cardiovascular endpoints were evaluated by a blinded adjudication committee. This was also a well-powered study of 18,325 patients with a predefined primary CV safety endpoint.

5.2.1.3 Summary of Postmarketing RCTs with Thromboembolic Data

From the two clinical studies published after 2005 reporting MI and stroke safety data during naproxen use, there is no evidence of a statistically significant increase in cardiovascular risk in the naproxen treatment groups. The only statistically significant result, reported in the TARGET naproxen substudy, showed that naproxen has a lower risk of composite CV outcome compared to lumiracoxib in OA patients with a high baseline CV risk who are not on aspirin.

Table 5-1: Summary of Post-2005 Randomized Controlled Trials on Naproxen Reporting Hazard Rates Thromboembolic Events

Author/ Year/ Country	N (PY)	Population	History of CHD	Events of Interest	Comparator (Dose)	HR for naproxen	95% CI	*P*-Value
Naproxen total daily dose ≤600-660 mg								
ADAPT 2006 (USA) [11]	2,528 (4,660 PY)	Age ≥70 yrs with a family history of Alzheimer's dementia	Included	MI	Placebo	1.49	0.69-3.22	0.31
				Stroke	Placebo	2.13	0.81-5.60	0.12
Naproxen total daily dose >600-660 mg								
Farkouh 2007 (TARGET post hoc; International) [13]	18,325	Primary osteoarthritis with **low** CV risk **not** using ASA	Excluded	Composite: MI, Stroke, CV death	Lumiracoxib (400 mg) [a]	0.88	0.43-1.78	0.714
		Primary osteoarthritis with **high** CV risk **not** using ASA	Included	Composite: MI, Stroke, CV death	Lumiracoxib (400 mg) [a]	Not applicable [b]	Not applicable	0.027

PY, Patient-years; CHD, Coronary heart disease; HR, Hazard ratio for naproxen; CI, Confidence interval; ADAPT, Alzheimer's Disease Anti-inflammatory Prevention Trial; MI, myocardial infarction; TARGET, Therapeutic Arthritis Research and Gastrointestinal Event; ASA, aspirin; CV, cardiovascular;

[a] In the TARGET study, lumiracoxib was the experimental arm and naproxen was the comparator arm. For this table the HR has been recalculated to represent naproxen vs. lumiracoxib.

[b] In patients at high CV risk without low-dose aspirin, there were no composite CV event in the naproxen group (n=335) vs. 5 events in the lumiracoxib group (n=318).

5.2.2 Observational Studies (2006-2013)

5.2.2.1 Observational Studies with Naproxen Total Daily Doses ≤600-660 mg

Six observational studies conducted after 2005 measured the risk of a thromboembolic event in patients exposed to OTC doses of naproxen (**Table 5-2**). Four of these studies used no NSAID exposure as a comparator, and reported a decrease in the risk of a thromboembolic events, though the results were not statistically significant.[14-17] A single study reported non-significant increase in the risk of thromboembolic events.[18]

Only a single study reported a significant increase in rehospitalization for AMI in patients exposed to low-dose naproxen.[14] This was a Danish case-crossover study (n=107,092) that measured the risk of rehospitalization for CHF or AMI in patients exposed to naproxen (≤500 mg total daily dose) or other NSAIDs after a previous hospitalized CHF event.[19] This study, using data from Danish registries linking hospitalizations and prescriptions, assessed the safety of COX-2 selective inhibitors and nonselective NSAIDs when used in patients following a first hospitalization for CHF by comparing the 0-30 days before hospitalization to the 90-120 days before hospitalization. The conditional logistic regression analysis yielded a statistically significant increase in MI events in patients exposed to low-dose naproxen (HR 1.47, 95% CI: 1.02-2.10; p=0.04). It should be noted that a number of distinct drugs were examined in this analysis separately and similar statistically significant results were observed in all other NSAIDs included in the study. Importantly, it is well recognized that prior CHD is a strong driver for a subsequent CV event, and this study includes only patients who have already experienced CHF. Lastly, this study relies on prescription data and estimates the total daily dose from 3 consecutive prescriptions, however, the possibility that some patients did not follow the recommended dose of naproxen cannot be excluded.

There were two studies reporting on the risk of stroke events, both of which reported a non-significant lower risk of stroke events during use of low doses of naproxen than no NSAID use (HR 0.89, 95% CI: 0.67-1.18 [15] and RR 0.62, 95% CI: 0.32-1.18 [17]).

5.2.2.2 Observational Studies with Naproxen Total Daily Doses >600-660 mg

Twenty-nine observational studies conducted after 2005 measured the risk of a thromboembolic event in patients exposed to high doses of naproxen (typically total daily doses >750 or >1000 mg) (**Table 5-2**). These include 17 studies assessing MI events,[16,18-33]10 studies assessing stroke events,[15,17,20,23,25,28,34-37] and 8 studies assessing composite CV outcome that included MI and/or stroke events.[14,15,17,37-41]

Of the 17 observational studies assessing the risk of MI events, 3 studies reported statistically significant decreases in MI events (1 naproxen vs. no NSAID; 2 naproxen vs. other NSAID),[28,30,33] while 5 studies reported statistically significant increases in MI events during prescription dose naproxen (4 naproxen vs. no NSAID; 1 naproxen vs. other NSAID).[20,22,24,25,31] There were 10 studies that reported non-significant increases in the risk of MI events in patients exposed to prescription doses of naproxen as compared to no NSAID or non-aspirin NSAIDs.[16,18,19,21,23-27,32]

Of the 10 observational studies assessing stroke events, 3 studies reported a decrease in the risk of ischemic stroke during use of prescription naproxen as compared to no NSAID or non-aspirin NSAIDs, although the findings were not statistically significant.[15,28,37] There were also 3 studies

reporting a non-significant increase in the risk of ischemic stroke.[23,34,37] However, 4 studies reported statistically significant increases in ischemic stroke events during use of prescription dose naproxen compared to no NSAID.[17,20,25,36] Two studies reported statistically significant increases in the risk of all stroke events during prescription naproxen use, but the CV events included non-thromboembolic events such as hemorrhagic strokes.[34,36] A single case cross-over study examining the 30 days prior to hospitalization for stroke in comparison to the 91-120 days prior to hospitalization also reported a statistically significant increase in stroke hospitalizations during exposure to prescription dose naproxen.[35]

Three studies reported statistically significant decreased CV composite endpoints during naproxen use in comparison to placebo [41,42] and other NSAIDs,[40] and 6 studies also reported decreases in CV composite endpoints that were not statistically significant,[14,15,38-40,42] A single study assessing the risk of composite events of AMI and CHD death in patients with a history of a hospitalized MI event did report a statistically significant increase in risk during prescription dose naproxen as compared to no NSAID use.[17]

It is important to note that all observational studies that reported a statistically significant increase in thromboembolic events during prescription dose naproxen versus no NSAID, except for Lee *et al.*, 2007, did not exclude patients with pre-existing CHD which can confound the study results if not properly adjusted for.[17,22,25,31,36]

Lee and colleagues conducted a nested-case control study with US veterans and their dependents, close to half of which were aged ≥75 years.[25] The odds that patients will experience an MI or stroke were compared among naproxen users versus NSAID nonusers, and were stratified by a history of CHD. In patients without a history of CHD, the risk of an MI (OR 1.21, 95% CI: 1.04-1.40) and stroke (OR 1.15, 95% CI: 1.01-1.31) were increased in the high-dose naproxen group. In patients with a history of CHD, the risk of an MI (OR 1.01, 95% CI: 0.84-1.20) and stroke (OR 1.20, 95% CI: 1.01-1.43) were also increased in the high-dose naproxen group, though not statistically significant for MI. There are several limitations of this study that should be noted. First, almost half of the study population was aged ≥75 years, an age group that has increased incidence of CV adverse events. Additionally, only patients receiving one NSAID prescription during the follow-up period were selected and may have led to some selection bias. The classification of patients as having pre-existing CHD was not based on clinical markers, but rather diagnostic codes; however, patients with a prior MI or stroke event were excluded. Therefore the CHD subcohort is not truly representative of the underlying comorbidity in this age group within the general population. This study relies on prescription data (as opposed to dispensing or medication use data) and estimates the total daily dose from 3 consecutive prescriptions. Therefore, the possibility that some patients did not fill their prescriptions for naproxen cannot be excluded. Lastly, some of the drug exposure groups have small sample sizes. Interestingly, another outcome that was measured was all-cause mortality for which NSAIDs combined showed a reduced risk. This complicates the interpretation when there is an observed increase in the risk of potentially fatal CV events during exposure to a drug or drug class, but then the drug or drug class is also shown to reduce the risk of all-cause death.

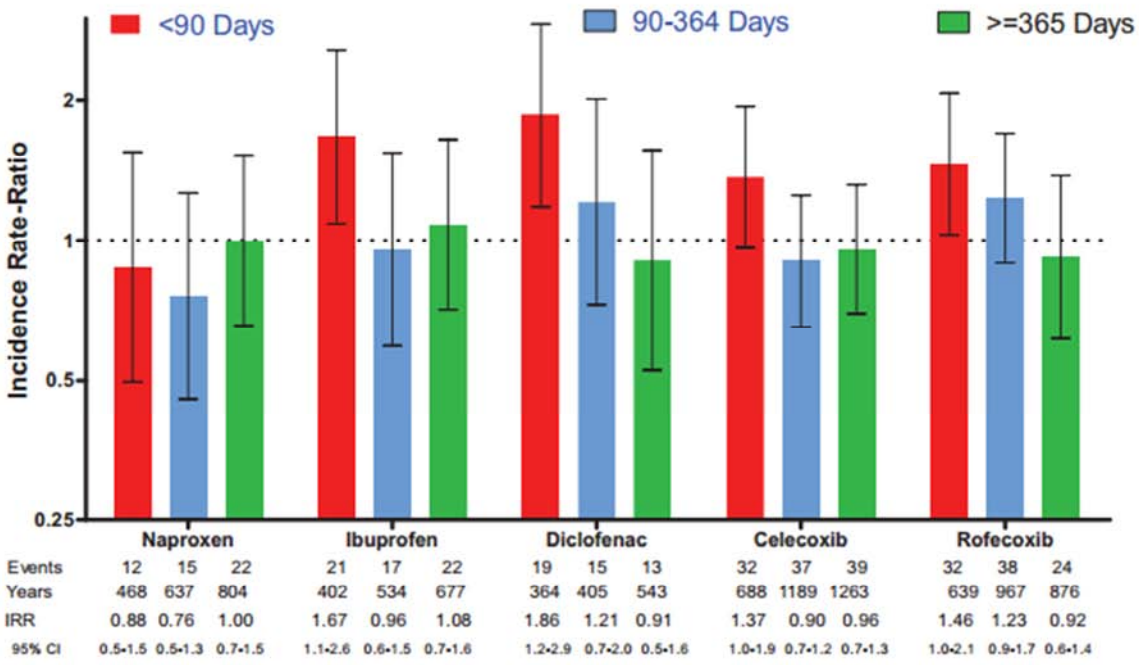
There are statistically significant findings indicating that naproxen use at doses >600-660 mg has a reduced risk for MI and stroke events compared to other non-aspirin NSAIDs, such as ibuprofen, diclofenac, celecoxib, and rofecoxib.[30,33,40]

5.2.2.2.1 Observational Studies With Data on Duration of Naproxen Use

There were 8 studies that reported on the risk of thromboembolic events based on duration of exposure to naproxen.[24,26,28,33,37,39,40,42] Two studies that compared patients with increasing number of prescriptions of naproxen (e.g., 2-4, 5-9, 10-19, ≥20 prescriptions) to those with a single prescription of naproxen, reported non-significant increases in the risk of MI.[24,26] Two additional studies that evaluated the risk of stroke[37] and composite outcome of MI, stroke, and CHD death[42] in groups of new users of naproxen (i.e., <1 year use of naproxen) and all users of naproxen, yielded non-significant results with no statistical differences in risk between both groups of users as well. One study reported that the risk ratios for MI or stroke observed in the first 60 days of naproxen use were very similar to those at ≥60 days of use (RR not reported; p>0.8 difference in drug exposure and baseline risk of CV event).[28] A multi-national study conducted by Ray *et al.* (2009) examined the incidence of serious CHD according to duration of naproxen use (**Figure 5-1**) and found that the adjusted rates did not vary with exposure time in current naproxen users while the rates did increase in patients that were using ibuprofen and selective COX-2 inhibitors for <90 days.[40]

Two studies reported the temporal risk of AMI[33]or composite outcome of MI, stroke, and CHD death[39]compared to non-aspirin NSAIDs. The post hoc temporal assessment by Motsko and colleagues (2006) reported non-significant differences in the composite outcome at varying exposure times when comparing prescription naproxen use to ibuprofen use (naproxen vs. ibuprofen >60 days use: HR 0.82, 95% CI: 0.42-1.63; >240 days use: HR 0.88, 95% CI: 0.19-4.09).[39] A time-to-event (MI diagnosis) analysis by Warner *et al.* (2008) plotted against cumulative incidence demonstrated that while there was a linear increase in MI rates over time during any NSAID use, after 24 months of exposure, the rates were significantly higher for celecoxib and rofecoxib than naproxen.[33]

Figure 5-1: Occurrence of coronary heart disease (CHD) by total duration of NSAID current use



Source: *Ray et al., 2009* [40]

5.2.2.2.2 Observational Studies Stratifying Prescription Naproxen Users by Low and High CV Risk at Baseline

There were 4 studies that reported on the risk of thromboembolic events based on pre-existing CV risk (i.e., at baseline) during exposure to prescription naproxen.[14,20,21,25] Each of the studies used different markers for assessing pre-existing CV risk, however all 4 studies did not find any differences in the risk for thromboembolic events during prescription naproxen use between patients at low CV risk versus patients at high CV risk. Three of these studies assessed the risk of MI events,[20,21,25] and though the MI risk was not statistically significant between the low and high CV risk groups, a single study did show that the risk of MI events during naproxen use reached statistical significance only in the high CV risk group.[25] Two studies assessed the risk of stroke events, with no observed differences in the stroke risk between low and high CV risk groups.[20,25] A single study assessing the risk of composite CV events compared patients with no CV-related hospitalization in the past 10 years (i.e., low CV risk) to patients with no hospitalization in the prior 5 years, and found no difference in the two CV risk groups. However, the patients with a longer history of no CV-related hospitalizations reported a non-significant lower risk of CV events (HR 0.83, 95% CI: 0.21-3.30) while the patients with a more recent CV-related hospitalization reported a non-significant increased risk of CV events (HR 1.28, 95% CI: 0.95-1.74).[14]

5.2.2.3 Summary of Observational Studies with Thromboembolic Data

From the 35 observational studies published after 2005 that report thromboembolic safety data during naproxen use, there is little to no evidence of an increased CV risk in patients exposed to naproxen. The majority of the observational studies with OTC doses of naproxen did not reach

statistical significance for MI [14-18] and stroke.[15,17] A single study reported a statistically significant increase in MI during naproxen use (≤500 mg),[19] but it should be noted that this study included patients with a previous MI or other forms of CHD are already at higher risk for an MI or stroke.

A few studies reported a statistically significant increase in MI [17,20,22,24,25] or ischemic stroke [17,20,25,31,34-36] during exposure to prescription dose naproxen. However, they should be interpreted in context of the study population (e.g., confounding within populations who are mostly elderly or have a history of CHD), study design (e.g., diagnosis- and prescription-based studies used as surrogates for actual disease and treatment), and other limitations common to retrospective and observational studies. Interestingly, studies that stratified the data based on history of CHD report no statistically significant differences in the risk of MI or stroke during naproxen use in patients with CHD versus those without a history of CHD.[20,21,25,42] One consistent finding was a lower risk of MI and composite CV events [33,38-40], with naproxen in comparison to several individual COX-2 specific inhibitors and nonselective NSAIDs, and which most consistently reached statistical significance.[23,30,33,39,40]

Table 5-2: Summary of Post-2005 Observational Studies on Naproxen Reporting Risk of Thromboembolic Events

Author/ Year/ Country	Design	N (PY)	Population	Events of Interest	History of CHD	Comparator (Dose)	Risk for naproxen	95% CI	*P*-Value
Naproxen total daily dose ≤600-660 mg [a]									
Andersohn 2006; UK [a] [18]	Case-control	17,561	Aged ≥40 yrs with 1+ NSAID prescription	AMI	Included	No NSAID	RR: 1.19	0.79-1.80	R
Fosbol 2009; Denmark [b] [14]	Case-crossover	1,028,437	Aged ≥10 yrs with 1+ NSAID prescription not hospitalized in **5** yrs preceding	Composite: MI, Death	Included	No NSAID	HR: 0.90	0.76-1.06	NR
		153,465	Aged ≥10 yrs with 1+ NSAID prescription not hospitalized in **10** yrs preceding	Composite: MI, Death	Included	No NSAID	HR: 0.85	0.47-1.53	NR
Fosbol 2010; Denmark [a] [15]	Case-crossover	1,028,437	Aged ≥10 yrs with 1+ NSAID prescription not hospitalized in **5** yrs preceding	MI, Coronary death	Included	No NSAID	HR: 0.79	0.62-1.02	NR
				Stroke	Included	No NSAID	HR: 0.89	0.67-1.18	NR
Garcia Rodriguez 2008; UK [a] [16]	Nested case-control	716,395	Aged 50-84 yrs	MI	Included	No NSAID	RR: 0.90	0.50-1.60	NR
Gislason 2009; Denmark [b] [19]	Case-crossover	107,092	Aged ≥30 yrs initiated NSAID post-hospitalization due to HF	MI [d]	Included	Control period [e]	HR: 1.47	1.02-2.10	0.04
Olsen 2013; Denmark [a] [17]	Retrospective cohort	58,946	Patients with a prior hospitalized MI	AMI, CHD death	Included	No NSAID	RR: 1.14 [j]	0.90-1.45	NR
				Stroke	Included	No NSAID	RR: 0.62 [j]	0.32-1.18	NR
Naproxen total daily dose >600-660 mg									
Abraham 2007; USA	Retrospective cohort	384,322	Aged 65-99 years with 1+ NSAID prescription	AMI	Excluded	No NSAID	HR: 1.5	1.2-2.0	NR
					Included	No NSAID	HR: 1.6	1.3-2.1	NR

Author/ Year/ Country	Design	N (PY)	Population	Events of Interest	History of CHD	Comparator (Dose)	Risk for naproxen	95% CI	*P*-Value
20									
				Stroke	Excluded	No NSAID	HR: 2.0	1.4-2.7	NR
					Included	No NSAID	HR: 2.0	1.5-2.7	NR
Andersohn 2006; UK [a] 18	Nested case-control	17,561	Aged ≥40 yrs with 1+ NSAID prescription	AMI	Included	No NSAID	RR: 1.05	0.66-1.66	NR
Brophy 2007; Canada [c] 21	Nested case-control	42,879	Aged ≥66 yrs initiating NSAID: **no** previous MI	AMI	Included	No NSAID	RR: 1.18	0.75-1.84	NR
			Aged ≥66 yrs initiating NSAID: **yes** previous MI	AMI	Included	No NSAID	RR: 1.56	0.68-3.58	NR
Caughey 2011; Australia [c] 34	Retrospective cohort	162,065	Incident NSAID dispensing to veterans/widows (ave age 76 yrs; 60% male)	All stroke [d]	Included	1 yr before NSAID use	1.52 [d]	1.15-2.01	NR
				Ischemic stroke [d]	Included	1 yr before NSAID use	1.51 [e]	1.00-2.26	NR
Chang 2010; Taiwan [c] 35	Case-cross over	28,424	Aged ≥20 yrs with hospitalized stroke	Ischemic stroke	Included	Control period [f]	OR: 1.46	1.22-1.74	NR
Cunnington 2008; USA 38	Retrospective cohort	80,826 (121,104 PY)	OA	MI, Ischemic stroke	Included	Other NSAID	HR: 0.99	0.64-1.54	NR
Fosbol 2009; Denmark [b] 14	Case-crossover	1,028,437	Aged ≥10 yrs with 1+ NSAID prescription not hospitalized in **5** yrs preceding	Composite: MI, Death	Included	No NSAID	HR: 1.28	0.95-1.74	NR
		153,465	Aged ≥10 yrs with 1+ NSAID prescription not hospitalized in **10** yrs preceding	Composite: MI, Death	Included	No NSAID	HR: 0.83	0.21-3.30	NR
Fosbol 2010; Denmark [b]	Case-crossover	1,028,437	Aged ≥10 yrs with 1+ NSAID prescription not	MI, Coronary death	Included	No NSAID	HR: 0.58	0.30-1.13	NR

Author/ Year/ Country	Design	N (PY)	Population	Events of Interest	History of CHD	Comparator (Dose)	Risk for naproxen	95% CI	*P*-Value
[15]			hospitalized in **5** yrs preceding	Stroke	Included	No NSAID	HR: 0.89	0.48-1.66	NR
Garcia Rodriguez 2008; UK [a] [16]	Nested case-control	716,395	Aged 50-84 yrs	MI	Included	No NSAID	RR: 1.12	0.74-1.69	NR
Gislason 2009; Denmark [b] [19]	Case-crossover	107,092	Aged ≥30 yrs initiated NSAID post-hospitalization due to HF	MI [d]	Included	Control period [f]	HR: 1.62	0.97-2.72	0.07
Haag 2008; Netherlands [c] [36]	Prospective cohort	70,063	Rotterdam Study cohort: Stroke-free at baseline tracked for incident stroke	All Stroke	Included	NSAID never users	HR: 2.63	1.47-4.72	NR
				Ischemic stroke	Included	NSAID never users	HR: 2.65	1.23-5.69	NR
Helin-Salmivaara 2006; Finland [c] [22]	Case-control	172,258	Cases: First time MI patients	MI (First)	Included	No NSAID	OR: 1.19	1.02-1.38	NR
Huang 2006; Taiwan [c] [23]	Retrospective cohort	16,326	Aged ≥18 yrs	MI	Included	Celecoxib	HR: 1.02	0.94-1.10	0.71
				Stroke	Included	Celecoxib	HR: 1.02	0.97-1.08	0.41
Jick 2006; UK [c] [24]	Case-control	600,000	Aged 30-79 yrs with NSAID prescription	MI	Excluded recent	2-4 vs.1 naproxen Rx[g]	RR: 2.2	1.2-4.0	NR
						5-9 vs. 1 naproxen Rx [g]	RR: 0.2	0.02-1.3	NR
						10-19 vs. 1 naproxen Rx [g]	RR: 1.9	0.4-10.3	NR
						≥20 vs 1 naproxen Rx [g]	RR: 2.5	0.5-13.8	NR
Lee 2007; USA [c] [25]	Nested case-control	565,451	Veterans & dependents diagnosed with OA **with** CV disease	MI	Included	No NSAID	OR: 1.01	0.84-1.20	NR
				Stroke	Included	No NSAID	OR: 1.20	1.01-1.43	NR

Author/ Year/ Country	Design	N (PY)	Population	Events of Interest	History of CHD	Comparator (Dose)	Risk for naproxen	95% CI	*P*-Value
			Veterans & dependents diagnosed with OA **without** CV disease	MI	Excluded	No NSAID	OR: 1.21	1.04-1.40	NR
				Stroke	Excluded	No NSAID	OR: 1.15	1.01-1.31	NR
Mangoni 2010; Australia [c] [26]	Nested case-control	1,745,725 (3,862,931 PY)	Veterans & dependents aged ≥65 yrs	MI	Excluded	1-4 naproxen Rx vs. nonuser [h]	OR: 0.93	0.79-1.09	NR
						5-10 naproxen Rx vs. nonuser [h]	OR: 1.31	1.00-1.70	NR
						11-19 naproxen Rx vs. nonuser [h]	OR: 1.27	0.93-1.74	NR
						20+ naproxen Rx vs. nonuser [h]	OR: 1.19	0.74-1.92	NR
Motsko 2006; USA [c] [39]	Retrospective cohort	84,677 (122,683 PY)	Veterans & dependents aged ≥35 yrs using NSAID **≤ 180 days**	Composite: AMI, CHD death, Stroke	Included	Ibuprofen	HR: 1.15	0.35-3.77	0.54
			Veterans & dependents aged ≥35 yrs using NSAID **> 180 days**	Composite: AMI, CHD death, Stroke	Included	Ibuprofen	HR: 0.83	0.48-1.42	0.81
Rahme 2007; Canada [c] [27]	Retrospective cohort	510,871	Aged ≥65 yrs with 1+ prescription for NSAID	AMI	Included	Acetaminophen	HR: 1.16	0.89-1.51	0.50
Ray 2009; International [40]	Retrospective cohort	45,566 (111,162 PY)	Aged 40-89 yrs with prior hosp. for serious CHD	Serious CHD: MI, CHD death	Included	NAP <1000mg vs. No NSAID	RR: 1.22	0.74-1.99	0.433
						NAP <1000mg vs. Ibuprofen	RR: 0.79 [i]	0.46-1.33	0.377
						NAP <1000mg vs. Diclofenac	RR: 0.47 [i]	0.28-0.79	0.004
						NAP <1000mg vs. Celecoxib	RR: 0.83 [i]	0.55-1.27	0.390
						NAP <1000mg vs. Rofecoxib	RR: 0.69 [i]	0.46-1.04	0.080

Author/ Year/ Country	Design	N (PY)	Population	Events of Interest	History of CHD	Comparator (Dose)	Risk for naproxen	95% CI	*P*-Value
						NAP ≥1000mg vs. No NSAID	RR: 0.78 [i]	0.55-1.10	0.160
						NAP ≥1000mg vs. Ibuprofen	RR: 0.58 [i]	0.36-0.93	0.023
						NAP ≥1000mg vs. Diclofenac	RR: 0.81 [i]	0.46-1.41	0.448
						NAP ≥1000mg vs. Celecoxib	RR: 0.62 [i]	0.39-0.99	0.046
						NAP ≥1000mg vs. Rofecoxib	RR: 0.44 [i]	0.24-0.81	0.008
Roumie 2008; USA [37]	Retrospective cohort	336,906 (989,826 PY)	Aged 50-84 yrs (Tennessee); **All** naproxen users	Stroke	Included	No NSAID	HR: 0.94	0.80-1.11	NR
			Aged 50-84 yrs (Tennessee); **<1 yr** naproxen use	Stroke	Included	No NSAID	HR: 1.02	0.73-1.42	NR
Roumie 2009; USA [42]	Retrospective cohort	610,001	Aged 39-94 yrs (Tennessee); **All** naproxen users	AMI, Stroke, CHD death [d]	Excluded	No NSAID	HR: 1.00	0.91-1.11	NR
					Included	No NSAID	HR: 0.88	0.79-0.99	NR
			Aged 39-94 yrs (Tennessee); **<1 yr** naproxen use	AMI, Stroke, CHD death [d]	Excluded	No NSAID	HR: 1.01	0.86-1.18	NR
					Included	No NSAID	HR: 0.98	0.82-1.16	NR
Olsen 2013; Denmark [a] [17]	Retrospective cohort	58,946	Patients with a prior hospitalized MI	AMI, CHD death	Included	No NSAID	RR: 1.99 [j]	1.44-2.73	NR
				Stroke	Included	No NSAID	RR: 2.59 [j]	1.49-4.51	NR
Solomon 2006; USA [k] [43]	Retrospective cohort	29,662	Low-moderate income insurance beneficiaries	MI	Included	No NSAID	RR: 0.67	0.45-0.98	NR
				Stroke	Included	No NSAID	RR: 0.83	0.67-1.04	NR
Solomon 2008; USA [c] [41]	Retrospective cohort	56,786	Low-moderate income insurance beneficiaries	Composite: MI, Stroke, CHF, and CV death	Included	No NSAID	HR: 0.79	0.67-0.93	NR

Author/ Year/ Country	Design	N (PY)	Population	Events of Interest	History of CHD	Comparator (Dose)	Risk for naproxen	95% CI	*P*-Value
Suissa 2006; USA [c] [29]	Case-control	6,138	RA	AMI	Included	No NSAID	RR: 0.98	0.59-1.64	NR
van der Linden 2009; Netherlands [30]	Nested Case-control	485,059	NSAID users	AMI	Included	Celecoxib	OR: 0.48	0.26-0.87	NR
van Staa 2008; UK [31]	Retrospective cohort	729,294	Aged ≥40 yrs prescribed traditional NSAID	MI	Included	NAP <1000 mg vs. No NSAID	RR: 1.19	1.01-1.40	NR
						NAP 1000 mg vs. No NSAID	RR: 1.31	1.15-1.48	NR
						NAP >100 mg vs. No NSAID	RR: 1.14	0.61-2.11	NR
Varas-Lorenzo 2009; Canada [32]	Nested case-control	23,254	Aged 40-84 yrs	AMI	Included	NAP ≤1000 mg vs. No NSAID	OR: 0.62	0.24-1.59	NR
						NAP >1000 mg vs. No NSAID	OR: 2.10	0.79-5.36	NR
Warner 2008; USA [33]	Retrospective cohort	38,258	Veterans & dependents aged 65-99 yrs, new NSAID users	AMI	Included	Etodolac	OR: 0.76 [i]	0.46-1.23	0.27
						Rofecoxib	OR: 0.46 [i]	0.23-0.96	0.04
						Celecoxib	OR: 0.46 [i]	0.22-0.92	0.03

PY, Patient-years; CHD, Coronary heart disease; CI, Confidence interval; RR, Relative Risk for naproxen; HR, Hazard ratio for naproxen; OR, Odds Ratio for naproxen; NR, Not reported; CV, cardiovascular; AMI, Acute myocardial infarction; MI, Myocardial infarction; OA, Osteoarthritis; CHD, Coronary heart disease

[a] The low-dose naproxen group was defined as ≤750 mg.
[b] The low dose-naproxen use was defined as ≤500 mg and the high-dose naproxen use was defined as >500 mg.
[c] This is a prescription-based studies that did not specify a total daily dose of naproxen, but where the majority of patients are likely to be on high-dose naproxen.
[d] Outcome is for hospitalization for specified thromboembolic event.
[e] This study estimated an adjusted sequence ratio which examines the asymmetry in the distribution of the incident event before and after the initiation of a naproxen treatment within a 1-year time period.
[f] Case period was defined as 0-30 days before hospitalization; Control period was defined as 90-120 days before hospitalization.
[g] The comparison was between patients with >1 naproxen prescription versus those with only 1 recorded prescription for naproxen.
[h] The comparison was between patients with 1+ naproxen prescription versus NSAID nonusers.
[i] Naproxen was the comparator, and for this table the risk ratios have been recalculated to represent naproxen vs. placebo or other NSAID.
[J] Risk ratio was estimated from the crude incidence rates.
[k] Includes patients on low- and high-dose naproxen.

5.2.3 Meta-analyses (2006-2013)

There were nine meta-analyses that have been published in which pooled risk ratios or odds ratios of thromboembolic events during exposure to naproxen versus placebo or comparator NSAID were examined; six publications were meta-analyses of RCTs (**Table 5-3**)[44-49] and 3 were meta-analyses of observational studies (**Table 5-4**).[50-52]

5.2.3.1 Meta-analyses of Randomized Controlled Trials (RCTs)

5.2.3.1.1 Meta-analyses of RCTs with Varying Doses of Naproxen

Three meta-analyses of RCTs after 2005 measured the pooled risk of MI, stroke, or a composite of CV events during exposure to any dose of naproxen.[44-46] All of the studies used in the meta-analyses were from RCTs comparing COX-2 selective inhibitors to variable doses of naproxen (i.e., naproxen was the comparator).[g] The majority of these analyses indicate that use of naproxen is associated with a lower risk of thromboembolic events as compared to COX-2 selective inhibitors.

Pairwise comparisons of naproxen use with individual COX-2 selective inhibitors showed that patients on naproxen had reduced risk of MI or stroke in comparison to lumiracoxib (MI and stroke statistically non-significant), rofecoxib (MI statistically significant; stroke not statistically significant), and etoricoxib (MI not statistically significant; not measured for stroke).[44,45] These same meta-analyses reported the risk of MI during naproxen use is lower than celecoxib (pooled RR 0.79, 95% CI: 0.26-2.43) or neutral with valdecoxib (pooled RR 1.01, 95% CI: 0.23-4.35); In contrast, a statistically non-significant increase in stroke was reported (naproxen vs. celecoxib: pooled RR 2.04, 95% CI: 0.56-7.14; naproxen vs. valdecoxib: pooled RR 2.56, 95% CI: 0.45-14.29). It should be noted that these data came from studies with mixed study populations (e.g., arthritis or chronic lower back pain), with variable doses of NSAIDs, and where naproxen was primarily the comparator drug. The sample size for the studies with valdecoxib was relatively small, and therefore the pooled risk for naproxen versus valdecoxib show wide 95% confidence intervals.

Finally, naproxen had a statistically significantly lower risk of vascular adverse events compared to a combined group of selective COX-2 inhibitors (pooled RR 0.64, 95% CI: 0.49-0.83; p=0.0006) and MI (pooled RR 0.49, 95% CI: 0.34-0.71; p=0.0002), as well as a non-significant reduced risk of stroke (pooled RR 0.91, 95% CI: 0.61-1.37; p=0.7).

5.2.3.1.2 Meta-analyses of RCTs with Naproxen Total Daily Doses >600-660 mg

Three meta-analyses of RCTs published after 2005 measured the pooled risk of MI, stroke, or a composite of thromboembolic events during exposure to high-dose naproxen (total daily doses >600-660 mg).[47-49] Two of these studies were large meta-analyses providing very robust data from randomized clinical trials on the CV safety of non-aspirin NSAIDs.[47,49]

The Coxib and traditional NSAIDs Trialists' (CNT) Collaboration conducted a collaborative meta-analysis of individual participant data from 280 RCTs of NSAIDs versus placebo and 474 trials of one NSAID versus another NSAID. Similarly, Trelle and colleagues conducted a large-scale meta-analysis of 31 randomized clinical trials comparing specific NSAIDs to placebo or to

[g] These meta-analyses did not report the pooled risk estimates by naproxen dose.

other NSAIDs. The CNT Collaboration (2013) and Trelle *et al.* (2011) studies included trials with long-term exposure to NSAIDs, at least 4 weeks duration or 100 patient-years follow-up, respectively. The main objective for both studies was to characterize and quantify the CV risk (and GI risk for the CNT Collaboration) of specific NSAIDs.

The CNT Collaboration (2013) found that the risk of major vascular events when compared to placebo was significantly increased by coxibs and diclofenac and non-significantly increased by ibuprofen; However , the risk of major vascular events was not increased by naproxen use (pooled RR 0.93, 95% CI: 0.69-1.27; p=0.66) (**Figure 5-2**).[47] Additionally, prescription dose of naproxen use was associated with statistically significant lower risk of major vascular events compared to COX-2 selective inhibitors (pooled RR 0.67, 95% CI: 0.52-0.86).

Using a meta-analysis from studies comparing use of prescription doses of naproxen to placebo or no NSAID (**Figure 5-**3), Trelle and colleagues (2011) reported non-significant pooled risk ratios for MI (pooled RR 0.82, 95% CI: 0.37-1.67) and stroke (pooled RR 1.76, 95% CI: 0.91-3.33).[49] The pooled analyses looking at a composite of major vascular events was reported to be non-significantly increased during naproxen use compared to placebo (pooled RR 1.22, 95% CI: 0.78-1.93).

Finally, pairwise comparisons of chronic exposure to prescription dose of naproxen (1000 mg) with chronic exposure to etoricoxib (60-120 mg) showed a statistically non-significant reduced risk of thromboembolic events in a variety of study populations.[48] The reduced risk of thrombotic events in patients on high-dose naproxen versus etoricoxib is observed regardless of patients' baseline CV risk.

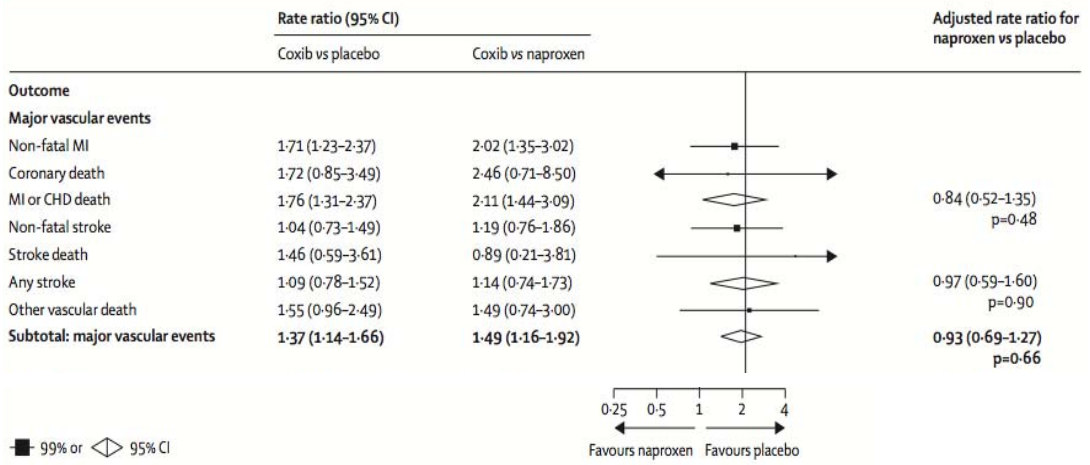
5.2.3.2 Summary of Meta-analyses of RCTs with Thromboembolic Data

Overall, naproxen exhibits the lowest CV risk for thromboembolic events such as MI and stroke as well as for composite CV outcome among non-aspirin NSAIDs.

In meta-analyses of RCTs published after 2005 that report thromboembolic safety data during naproxen use, no statistically significant evidence was found for an increased risk of MI or major vascular events during the naproxen treatment compared to placebo or nonuse. All of the large meta-analyses of RCTs in patients exposed to any dose or prescription doses of naproxen compared to selective COX-2 inhibitors showed a reduced risk for a composite of CV events (1 statistically significant and 5 non-significant results) (**Figures 5-2 & 5-3)**.

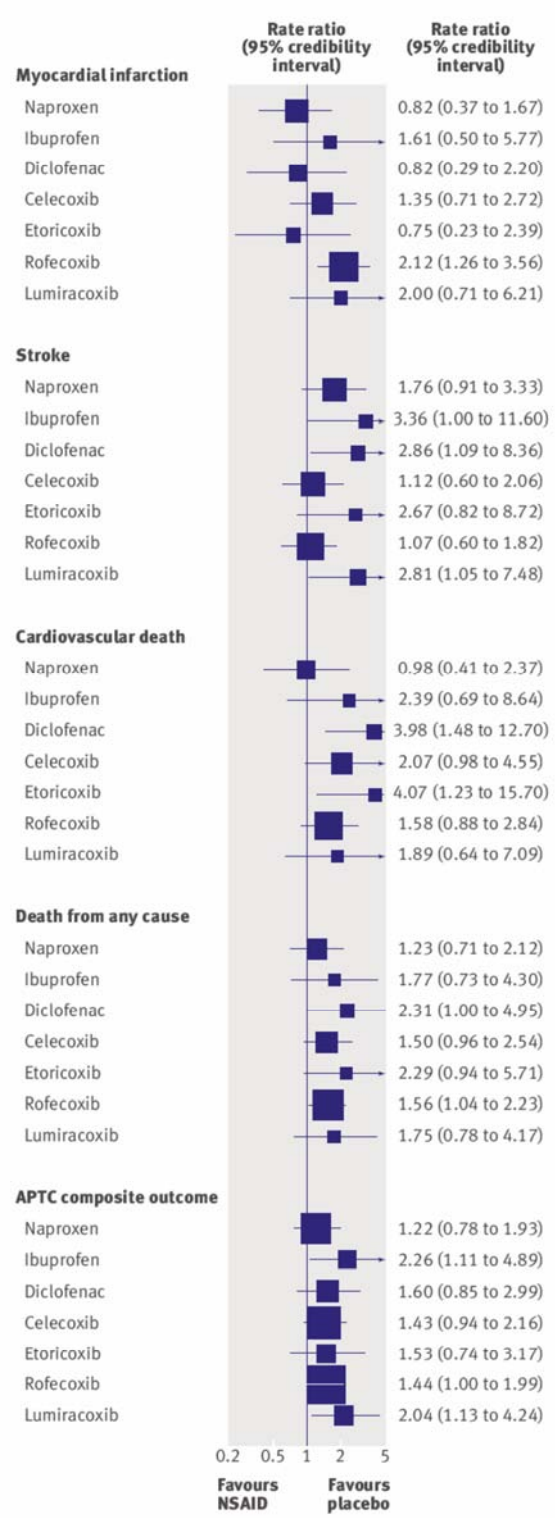
Similarly, no statistically significant evidence was found for an increased risk of stroke during naproxen use. There was a non-significant increase in stroke risk during naproxen use at doses >600-660 mg to placebo, and non-significant findings (i.e., both non-significant increase and decreases) for naproxen compared to COX-2 selective inhibitors.

Figure 5-2: Effects of Naproxen on Cardiovascular Events



Source: *Modified from CNT Collaboration, 2013* [47]

Figure 5-3: Estimates of Rate Ratios for NSAIDs Compared with Placebo



NSAID, non- steroidal anti-inflammatory drug; APTC, Antiplatelet Trialists' Collaboration
Source: *Trelle et al., 2007* [49]

Table 5-3: Summary of Post-2005 Meta-Analyses of RCTs with Naproxen Reporting Risk of Thromboembolic Events

Author/ Year	N (PY) [a]	Population	Events of Interest	Comparator (Dose)	Pooled RR or OR for naproxen	95% CI	*P*-Value
Naproxen total daily dose: Variable							
Chen 2006 [44]	11,183	Varies: Includes OA, RA, CLBP, CA, AD	Stroke	Celecoxib	2.04 [b]	0.56-7.14	NR
	10,958	Varies: See above	Stroke	Lumiracoxib	0.92 [b]	0.49-1.72	NR
	13,633	Varies: See above	Stroke	Rofecoxib	0.88 [b]	0.39-2.00	NR
	2,555	Varies: See above	Stroke	Valdecoxib	2.56 [b]	0.45-14.29	NR
Chen 2007 [45]	13,743	Varies: Includes OA, RA, CLBP, CA, AD	MI	Celecoxib	0.79 [b]	0.26-2.43	NR
	867	Varies: See above	MI	Etoricoxib	0.65 [b]	0.07-6.25	NR
	11,764	Varies: See above	MI	Lumiracoxib	0.63 [b]	0.32-1.23	NR
	13,633	Varies: See above	MI	Rofecoxib	0.19 [b]	0.07-0.48	<0.05
	2,332	Varies: See above	MI	Valdecoxib	1.01 [b]	0.23-4.35	NR
Kearney 2006 [46]	(27,338 PY)	Varies	Vascular events	Coxibs [c]	0.64 [b]	0.49-0.83	0.0006
			MI	Coxibs [c]	0.49 [b]	0.34-0.71	0.0002
			Stroke	Coxibs [c]	0.91 [b]	0.61-1.37	0.7
Naproxen total daily dose >600-660 mg or from a prescription-based study							
CNT Collaboration 2013 [47]	Entire study: 48,706	Varies	Major vascular events [d]	Placebo	0.93	0.69-1.27	0.66
				Coxibs [c]	0.67 [b]	0.52-0.86	NR
Curtis 2006 [48]	4,315 (2,287 PY)	OA, RA, AS, CLBP	Thrombotic events [e]	Etoricoxib (60-120 mg)	0.59 [b]	0.31-1.10	NR
		OA, RA, AS, CLBP with **high** CV risk	Thrombotic events [e]	Etoricoxib (60-120 mg)	0.53 [b]	0.21-1.37	NR
		OA, RA, AS, CLBP with **low** CV risk	Thrombotic events [e]	Etoricoxib (60-120 mg)	0.63 [b]	0.28-1.45	NR

Author/ Year	N (PY) [a]	Population	Events of Interest	Comparator (Dose)	Pooled RR or OR for naproxen	95% CI	*P*-Value
	1,089	OA	Thrombotic events [e]	Etoricoxib (60-120 mg)	0.60 [b]	0.22-1.64	NR
	1,988	RA	Thrombotic events [e]	Etoricoxib (60-120 mg)	0.71 [b]	0.31-1.64	NR
Trelle 2011 [49]	30,472	Varies: AD, OA, RA	MI	Placebo	0.82	0.37-1.67	NR
			Stroke	Placebo	1.76	0.91-3.33	NR
			APTC composite [d]	Placebo	1.22	0.78-1.93	NR

PY, Patient-years; RR, Relative risk for naproxen; OR, Odds ratio for naproxen; CI, Confidence intervals; NR, Not reported; OA, Osteoarthritis; RA, Rheumatoid arthritis; AS, Ankylosing spondylitis; CLBP, Chronic low back pain; CA, Colorectal adenoma; AD, Alzheimer's disease; MI, Myocardial infarction; CV, cardiovascular; APTC, Antiplatelet Trialists' Collaboration

[a] Population size refers to naproxen and comparator samples only.

[b] Naproxen was the comparator, and for this table the pooled OR or RRs have been recalculated to represent naproxen vs. placebo or other NSAID.

[c] Coxibs include celecoxib, rofecoxib, etoricoxib, lumiracoxib, and valdecoxib.

[d] 'Major vascular events' in the CNT Collaboration 2013 and Kearney 2006 studies was defined as APTC composite (nonfatal MI, nonfatal stroke, or death from a vascular cause); major coronary events (nonfatal MI or death from coronary disease); and stroke (hemorrhagic, ischemic, or unknown).

[e] 'Thrombotic events' were defined as: cardiac, cerebrovascular, and peripheral vascular events such as unstable angina, myocardial infarction, ischemic stroke, and transient ischemic attacks. It does not include fatal hemorrhagic deaths or hemorrhagic stroke.

5.2.3.3 Meta-analyses of Observational Studies

5.2.3.3.1 Meta-analyses of Studies with Varying Doses of Naproxen

From four post-2005 meta-analyses of observational studies that reported risk of thromboembolic events during any dose naproxen use,[h] there is no statistically significant confirmation of an increased MI or stroke risk in patients exposed to naproxen. Two meta-analyses reported pooled risk ratios from studies comparing naproxen use at variable doses to no NSAID use for MI (pooled RR 0.98, 95% CI: 0.92-1.05)[10] and AMI (pooled RR 1.06, 95% CI: 094-1.20)[53] and stroke (pooled RR 1.14, 95% CI: 0.76-1.69).[50,52] Varas-Lorenzo *et al.* (2013) also reported no significant difference in risk of AMI during naproxen use between patients already at high risk for AMI (pooled RR 1.13, 95% CI: 0.87-1.46) and low and high AMI risk patients combined.[53]

5.2.3.3.2 Meta-analyses of Studies with Naproxen Total Daily Doses >600-660 mg

A large meta-analyses of observational studies (>2.7 million exposed patients), published after 2005, measured the pooled risk of the composite outcome of MI, stroke, and CV death during exposure to prescription doses of naproxen compared to no NSAID use (pooled RR 1.09, 95% CI: 1.02-1.16).[51] In addition, in their review of several extensively studied (≥10 studies each) non-aspirin NSAIDs, the authors concluded that naproxen and low-dose ibuprofen are least likely to increase CV risk, while the highest overall risks were seen with rofecoxib and diclofenac. Additionally, a subset analysis also showed that the risk of CV events during naproxen use was neutral at all doses. In contrast the risk of CV events was elevated at low doses rofecoxib and diclofenac and the risk increased for both drugs with higher doses. An increased risk of CV events was even observed with high doses of ibuprofen.

A recent meta-analysis with estimated a relative risk of AMI of 0.93 (95%:0.75-1.16) associated with low dose naproxen and 0.97 (95%CI:0.80-1.16) with high dose naproxen use.[53] The authors concluded that, except for naproxen, higher risk was generally associated with higher doses of NSAID.

5.2.3.4 Summary of Meta-analyses of Observational Studies with Thromboembolic Data

When assessing MI or stroke separately, there is no statistically significant evidence of an increased risk of MI or stroke during naproxen use from the three meta-analyses of observational studies published after 2005. A decreased risk for MI and increased risk for stroke were reported during naproxen use (at variable doses) compared to no NSAID use, but were not statistically significant for either outcome. However, a single study did report that prescription doses of naproxen were associated with a statistically significant increased risk for the composite CV outcomes of MI, stroke and CV death. Overall, naproxen exhibits the lowest risk among non-aspirin NSAIDs for the composite of CV events.

[h] These meta-analyses did not report the pooled risk estimates by naproxen dose.

Table 5-4: Summary of Post-2005 Meta-Analyses of Observational studies with Naproxen Reporting Risk of Thromboembolic Events

Author/ Year	N (PY)	Population	Events of Interest	Comparator (Dose)	Pooled RR or OR for naproxen	95% CI	*P*-Value
Naproxen total daily dose: Variable							
Hernandez-Diaz 2006 [50]	Not reported	Varies	MI	No NSAID	0.98	0.92-1.05	NR
Varas-Lorenzo 2011 [52]	Not reported	Not reported	Stroke	No NSAID	1.14	0.76-1.69	NR
Varas-Lorenzo 2013 [53]	6 studies with low and high dose naproxen users	Varies with **Low or High risk** of AMI	AMI	No NSAID	1.06	0.94-1.20	NR
		Varies with **High risk** of AMI	AMI	No NSAID	1.13	0.87-1.46	NR
Naproxen total daily dose ≤600-660 mg							
Varas-Lorenzo 2013 [53]	5 studies with low dose naproxen users	Varies	AMI	No NSAID	0.93	0.75-1.16	NR
Naproxen total daily dose >600-660 mg or from a prescription-based study							
McGettigan 2011 [51]	>2,700,000 exposed patients	Varies	MI, stroke, CV death	No NSAID	1.09	1.02-1.16	NR
Varas-Lorenzo 2013 [53]	6 studies with high dose naproxen users	Varies	AMI	No NSAID	0.97	0.80-1.16	NR

PY, Patient-years; RR, Relative risk for naproxen; OR, Odds ratio for naproxen; CI, Confidence intervals; NR, Not reported; MI, Myocardial infarction; CV, cardiovascular

5.3 Congestive Heart Failure (CHF)

5.3.1 Postmarketing Randomized Controlled Trials (RCTs) (2006-2013)

Included in our previous briefing book and presented at the 2005 Advisory Committee meeting, were two clinical safety studies that have since been published and in which risk (hazard rates) (**Table 5-5**) of CHF during exposure to naproxen versus a placebo or comparator NSAID were examined.

5.3.1.1 ADAPT (2006)

Despite limitations of the study, there is no suggestion of a statistically significant increased risk of CHF with naproxen.

In the ADAPT study, patients with a family history of Alzheimer's dementia were randomized to celecoxib (200 mg twice daily), or active comparator naproxen sodium (220 mg twice daily), or placebo (as previously described in Section 5.2.1.1).[11] Patients were followed for 1-46 months (median follow up times = naproxen 23.5 months and placebo 22.1 months), and patient-reported occurrence of CV death, MI, stroke, CHF, or TIA were recorded. The study suggested a non-significant increased risk of CHF (HR 1.70, 95% CI: 0.62-4.69, p=0.30) for patients using naproxen versus those on placebo. While the ADAPT study is the only long-term placebo-controlled trial with multi-dose naproxen since 2005, there are several serious issues to note regarding the study design and overall generalizability of the study results. First, the ADAPT study was designed to measure the primary efficacy endpoint, prevention of Alzheimer's disease, and was not powered to detect statistical differences in CV and CVA events.[i] This is also reflected in the low number of events in the trial. Second, there were major limitations in extending the results of the ADAPT study population, who are primarily elderly patients likely to have different risk factors than the general population. Finally and importantly, the patient-reported CV events were not clinically adjudicated, which places the accuracy of the incident events into question.

5.3.1.2 TARGET Naproxen Substudy (2007)

The TARGET study evaluated the safety of lumiracoxib (400 mg once daily) versus high-dose naproxen (500 mg twice daily) or lumiracoxib (400 mg once daily) versus ibuprofen (800 mg three times daily) for 52 weeks in patients with osteoarthritis (as previously described in Section 5.2.1.2).[12] The study was designed for the primary endpoints of gastrointestinal events and a composite endpoint of MI, stroke and CV death. However, data on CHF events were also collected and assessed. In a post-hoc analysis, the naproxen substudy evaluated risk of the composite CV event based on the patients' baseline CV risk and on use of low-dose aspirin.[13] The Cox proportional hazards model yielded non-significant increased risk of CHF for non-aspirin users of naproxen as compared to lumiracoxib users with either low baseline CV risk (HR 1.77, 95% CI: 0.42-7.40, p=0.322) or high baseline CV risk (HR 2.17, 95% CI: 0.20-24.19, p=0.435). As it was not a primary endpoint, CHF events were not clinically adjudicated.

[i] All treatment arms of the ADAPT study were prematurely suspended after increased cardiovascular risks with celecoxib were reported from the National Cancer Institute-sponsored Adenoma Prevention with Celecoxib (APC) trial.

5.3.1.3 Summary of Postmarketing RCTs with CHF Data

From the two clinical studies published after 2005 reporting MI and stroke safety data during naproxen use, there is no statistically significant confirmation of an increased risk of CHF in the naproxen treatment groups. Both studies were limited in their design for measuring CHF outcomes.

Table 5-5: Summary of Post-2005 Randomized Controlled Trials on Naproxen Reporting Hazard Rates of Congestive Heart Failure

Author/ Year/ Country	N (PY)	Population	History of CHD	Events of Interest	Comparator (Dose)	HR for naproxen	95% CI	*P*-Value
Naproxen total daily dose ≤600-660 mg								
ADAPT 2006 (USA) [11]	2,528 (4,660 PY)	Age ≥70 yrs with a family history of Alzheimer's dementia	Not excluded	CHF	Placebo	1.70	0.62-4.69	0.30
Naproxen total daily dose >600-660 mg								
Farkouh 2007 (TARGET post hoc; International) [13]	18,325	Primary osteoarthritis with **low** CV risk **not** using ASA	Excluded	CHF	Lumiracoxib (400 mg) [a]	1.77	0.42-7.40	0.322
		Primary osteoarthritis with **high** CV risk **not** using ASA	Included	CHF	Lumiracoxib (400 mg) [a]	2.17	0.20-24.19	0.435

PY, Patient-years; CHD, Coronary heart disease; HR, Hazard ratio for naproxen; CI, Confidence interval; ADAPT, Alzheimer's Disease Anti-inflammatory Prevention Trial; CHF, Congestive heart failure; TARGET, Therapeutic Arthritis Research and Gastrointestinal Event; ASA, aspirin; CV, cardiovascular;

[a] In the TARGET study, lumiracoxib was the experimental arm and naproxen was the comparator arm. For this table the HR has been recalculated to represent naproxen vs. lumiracoxib.

5.3.2 Observational Studies (2006-2013)

There were two observational studies that have been published (**Table 5-6**) in which risk of CHF during exposure to naproxen versus a placebo or comparator NSAID was examined.[19,26]

5.3.2.1 Observational Studies with Naproxen Total Daily Doses ≤600-660 mg

One large Danish case-crossover study (n=107,092) conducted after 2005 (previously described in Section 5.2.2.1) measured the risk of rehospitalization for CHF in patients exposed to naproxen (≤500 mg total daily dose) or other NSAIDs after a previous hospitalized CHF event.[19] This study, using data from Danish registries linking hospitalizations and prescriptions, assessed the safety of COX-2 selective inhibitors and nonselective NSAIDs when used in patients following a first hospitalization for CHF by comparing the 0-30 days before hospitalization to the 90-120 days before hospitalization. The conditional logistic regression analysis yielded a statistically non-significant increase in the CHF event in patients exposed to low-dose naproxen (HR 1.18, 95% CI: 0.97-1.44; p=0.10). It should be noted that a number of distinct drugs were examined in this analysis separately and naproxen and ibuprofen appeared to have the lowest risk of a rehospitalization for CHF. Confounding due to pre-existing CHD in the study population cannot be excluded. Another limitation is that the daily dosage of naproxen was estimated from prescription claims and may not accurately reflect the dose of naproxen use.

5.3.2.2 Observational Studies with Naproxen Total Daily Doses >600-660 mg

The same Danish case-cross over study also examined the risk of rehospitalization for CHF in patients exposed to naproxen total daily doses >500 mg or other NSAIDs.[19] The conditional logistic regression analysis yielded a statistically non-significant increase in the CHF event in patients exposed to high-dose naproxen (HR 1.18, 95% CI: 0.88-1.57; p=0.27).

A second large observational study in Australia with a nested case-control design (n=1,745,725) in patients aged ≥65 years comparing the odds of patients with CHF having been exposed to one of more prescriptions of naproxen.[26] This study reported risk ratios that were not statistically significant [1-4 naproxen prescriptions vs. nonusers Odds Ratio (OR) 0.97, 95% CI: 0.87-1.09], though a statistically non-significant increase in the risk of CHF could be observed for patients with more prescriptions of high-dose naproxen (e.g., 20+ naproxen prescriptions vs. nonusers OR 1.40, 95% CI: 0.98-2.00). The authors concluded that use of naproxen was not associated with an increased risk of incident CHF.

5.3.2.3 Summary of Observational Studies with CHF Data

From the two observational studies published after 2005 that report CHF safety data during naproxen use, there is no statistically significant evidence of an increased CHF risk in patients exposed to naproxen for both OTC and prescription doses of naproxen. Further, these studies have limitations related to all observational studies. Additionally, limitations including discharge diagnosis data are not suitable for measuring incidence of CHF and the effect of unmeasured confounders cannot be excluded.

Table 5-6: Summary of Post-2005 Observational Studies on Naproxen Reporting Risk of Congestive Heart Failure

Author/ Year/ Country	Design	N (PY)	Population	Events of Interest	History of CHD	Comparator (Dose)	Risk for naproxen	95% CI	*P*-Value
Naproxen total daily dose ≤600-660 mg									
Gislason 2009; Denmark [a] [19]	Case-crossover	107,092	Aged ≥30 yrs initiated NSAID post-CHF	CHF [b]	Included	Control period [c]	HR: 1.18	0.97-1.44	0.10
Naproxen total daily dose >600-660 mg									
Gislason 2009; Denmark [a] [19]	Case-crossover	107,092	Aged ≥30 yrs initiated NSAID post-hospitalization due to HF	CHF [b]	Included	Control period [c]	HR: 1.18	0.88-1.57	0.27
Mangoni 2010; Australia [d] [26]	Nested case-control	1,745,725 (3,862,931 PY)	Veterans & dependents aged ≥65 yrs	CHF	Excluded	1-4 naproxen Rx vs. nonuser [e]	OR: 0.97	0.87-1.09	NR
						5-10 naproxen Rx vs. nonuser [e]	OR: 1.09	0.87-1.35	NR
						11-19 naproxen Rx vs. nonuser [e]	OR: 1.16	0.92-1.47	NR
						20+ naproxen Rx vs. nonuser [e]	OR: 1.40	0.98-2.00	NR

PY, Patient-years; CHD, Coronary heart disease; OR, Odds Ratio for naproxen; Relative Risk for naproxen; CI, Confidence interval; NR, Not reported; CV, cardiovascular; CHF, Congestive heart failure

[a] The low dose-naproxen use was defined as ≤500 mg and the high-dose naproxen use was defined as >500 mg.

[b] Outcome is for hospitalization for CHF.

[c] Case period was defined as 0-30 days before hospitalization; Control period was defined as 90-120 days before hospitalization.

[d] This is a prescription-based study that did not specify a total daily dose of naproxen, but where the majority of patients are likely to be on high-dose naproxen.

[e] The comparison was between patients with 1+ naproxen prescription versus NSAID nonusers.

5.3.3 Meta-analyses of Randomized Controlled Trials (RCTs) (2006-2013)

Since 2005, only one meta-analysis of RCTs reported data on the risk of CHF specific to naproxen use (**Table 5-7**).[47] This large meta-analysis (n=48,706) of RCTs reported a statistically significant increase in the risk of hospitalization due to CHF (RR 1.87, 95% CI: 1.10-3.16); p=0.0197) for patients using prescription doses of naproxen versus placebo; however, a non-significant difference in risk was observed when naproxen was compared to selective COX-2 inhibitors (RR 0.85, 95% CI: 0.56-1.32). The authors concluded that any NSAID use does increase the risk of CHF-related hospital admissions, but that COX-2 selective inhibitors and ibuprofen use are associated with the highest risk, while naproxen was associated with a lower risk.

Table 5-7: Summary of Post-2005 Meta-Analyses of RCTs on Naproxen Reporting Risk of Congestive Heart Failure (CHF)

Author/ Year	N	Population	Events of Interest	Comparator (Dose)	Pooled RR or OR for naproxen	95% CI	*P*-Value
Naproxen total daily dose >600-660 mg or from a prescription-based study							
CNT Collaboration 2013 [47]	Entire study: 48,706	Varies	CHF	Placebo	1.87	1.10-3.16	0.0197
				Coxibs [a]	0.85 [b]	0.56-1.32	NR

PY, Patient-years; RR, Relative risk for naproxen; OR, Odds ratio for naproxen; CI, Confidence intervals; NR, Not reported

[a] Coxibs include celecoxib, rofecoxib, etoricoxib, lumiracoxib, and valdecoxib.

[b] Naproxen was the comparator, and for this table the pooled OR or RRs have been recalculated to represent naproxen vs. placebo or other NSAID.

5.3.4 Summary of Postmarketing Studies Assessing CHF

Clinical trials are typically the most robust evidence of drug associations to outcomes. However, from the two clinical studies published after 2005 reporting CHF safety data during naproxen use, there was no statistically significant confirmation of an increased risk of CHF in the naproxen treatment groups. Both studies were limited in their design for measuring CHF outcomes.

The number of studies primarily designed to assess the safety of naproxen with respect to the risk of CHF developing is limited. Therefore, meta-analyses are a useful method for systematically quantifying findings from a group of methodologically related studies. A single meta-analyses of RCTs published after 2005 reported that any NSAID use does increase the risk of CHF-related hospital admissions, but that COX-2 selective inhibitors and ibuprofen use are associated with the highest risk, while naproxen was associated with a lower risk in comparison.

Observational studies are often limited by their retrospective design and can be subject to selection bias and confounding due to unmeasured factors. Despite these limitations, observational studies provide useful information on the real-world use of naproxen. Since there are a more extensive number of observational studies conducted in the postmarketing period than clinical studies, they are a primary source for detecting safety signals. Individually, these studies show no evidence of an increased CHF risk in patients exposed to naproxen at both low and high doses. However, in a single meta-analysis there was a significant increased risk for CHF for all NSAIDs, including naproxen, compared to placebo. There was a non-significant difference in risk when naproxen was compared to selective COX-2 inhibitors.

6. Postmarketing Reports of Myocardial Infarction and Cerebrovascular Accidents: Naproxen/Naproxen Sodium

6.1 Cardiovascular (CV) Events

6.1.1 Roche Safety Database Individual Case Safety Reports (ICSRs) of CV Events from 1973 to 2004

Naproxen, a nonsteroidal anti-inflammatory drug (NSAID) approved in 1976, is currently available in the United States (US) for both prescription use (marketed by Genentech, a member of the Roche Group) and over-the-counter (OTC) use (marketed by Bayer HealthCare LLC, Consumer Care).

From September 1973 to December 21, 2004, a total of 75,584 events were received into the Roche pharmacovigilance (PV) database for all naproxen products, including 4,018 (5.3%) events under the MedDRA System Organ Class (SOC) Cardiac disorders (about 22% of Cardiac disorders events were classified as serious). Patient exposure to Roche naproxen products for the period June 1, 1995 to December 21, 2004 was estimated at 113,188,125 patients.

From September 1973 to December 21, 2004, 71 ICSRs indicating the event of acute myocardial infarction (AMI)/ myocardial infarction (MI) were retrieved from the Roche PV database. To address well-known issues such as underreporting, case ascertainment and the determination of population-at-risk, proportional reporting ratios (PRRs) were calculated to aid in signal detection. A PRR indicates how frequently an adverse event (AE) is reported for a given drug

relative to all other drugs within a pharmacovigilance database. A PRR < 1 indicates less frequent reporting of an AE relative to other drugs, while a PRR > 1 indicates more frequent reporting.

PRRs were calculated for the MedDRA Higher Level Term (HLT) Ischaemic coronary artery disorders and for the individual Preferred Terms (PTs) Acute myocardial infarction and Myocardial infarction for naproxen (including naproxen sodium prescription and over-the-counter (OTC)), and did not indicate a signal during this period. These PRRs are displayed in **Table 6-1**.

6.1.2 Roche Safety Database ICSRs of CV Events from 2004 to 2013

For the period from December 22, 2004 to July 31, 2013, the total exposure to Roche prescription naproxen/sodium was estimated at 68,831,428 patients. During this time, a total of 28,048 events were reported.

During this period, 73 newly reported case reports of AMI/ MI were retrieved from the Roche PV database. Of these 73, 65 were from literature, 43 of which originated from a single article, a cross-over study included in section 5.2.2.2 of this report.[14]

In the manner described above, cumulative PRRs from 1973 to 2013 were calculated for the MedDRA High Level Term (HLT) Ischaemic coronary artery disorders and for the individual Preferred Terms (PTs) Acute myocardial infarction and Myocardial infarction. The PRRs for both event types were found to be < 1 for both the earlier time period and the cumulative interval and thus do not indicate a disproportionate reporting of these terms in the safety database.

Table 6-1: Roche PRR for CNS hemorrhages and cerebrovascular accidents

Event	1973 - 2004	1973 - 2013
AMI/ MI (PTs)	0.18	0.70
Ischaemic coronary artery disorders (HLT)	0.16	0.61

6.1.3 Bayer Safety Database ICSRs CV Events from 1994 to 2004

The estimated exposure to OTC oral naproxen sodium from 1994 to December 21, 2004 was 550,000,000 courses of therapy. A course of therapy is defined as two tablets per day for 10 days.

During this time period 13,355 ICSRs representing 25,268 coded events were retrieved from the Bayer PV database for oral naproxen sodium products. Of these 25,268 events, 1% (249) was reported under the SOC Cardiac disorders. About 49% (121) of the 249 cardiac events were classified as serious for adverse event reporting purposes.

For this interval, a total of 25 case reports of AMI/ MI were retrieved from the Bayer PV database. The PRRs were calculated for the HLT Ischaemic coronary artery disorders and for the PTs Acute myocardial infarction/ Myocardial infarction, and are displayed in **Table 6-2**. These data did not indicate a signal.

6.1.4 Bayer Safety Database ICSRs of CV Events from 2004 to 2013

The estimated exposures to oral naproxen sodium are based on sales data as presented in Bayer periodic safety update reports (PSURs). For the period of December 22, 2004 to August 1, 2013,

the total estimated exposure to oral naproxen sodium was 1,334,000,000 courses of therapy. A course of therapy is defined as two tablets per day for 10 days.

From December 22, 2004 to August 1, 2013, 72,902 ICSRs reporting 138,454 events were retrieved from the Bayer PV database for oral naproxen sodium products. Of these 138,454 events, 1% (1,441) was reported under the SOC Cardiac disorders. About 30% (431) of the 1,441 cardiac events were classified as serious.

For this interval, a total of 91 ICSRs reporting AMI/ MI were retrieved from the Bayer PV database. The PRRs were calculated for these PTs and for the HLT Ischaemic coronary artery disorders and are shown below in Table 2 along with their respective PRRs from the previous period.

Table 6-2: Bayer PRR for AMI/ MI and Ischaemic Coronary Artery Disorders

Event	1973 - 2004	2005 - 2013
AMI/ MI (PTs)	0.22	0.34
Ischaemic coronary artery disorders (HLT)	0.38	1.02

These PRRs indicate that there were no signals for either AMI/MI or Ischaemic coronary artery disorders over the entire post-marketing period by use of this method.

6.2 Central Nervous System (CNS) Hemorrhages and Cerebrovascular Accidents (CVAs)

6.2.1 Roche Safety Database ICSRs of CNS Hemorrhages and CVAs from 1973 to 2004

From September 1973 to December 21, 2004, 81 ICSRs were retrieved from the Roche PV database using the MedDRA HLT Central nervous system haemorrhages and cerebrovascular accidents under the SOC Nervous system disorders.

The PRR was calculated for the HLT Central nervous system haemorrhages and cerebrovascular accidents for naproxen (including naproxen sodium prescription and OTC) and is displayed in Table 3. No signal was indicated from these data based on the PRR method.

6.2.2 Roche Safety Database ICSRs of CNS Hemorrhages and CVAs from 2004 to 2013

From December 22, 2004 to July, 31 2013, a total of 36 newly reported cases for prescription naproxen/sodium were retrieved from the Roche PV database for the HLT Central nervous system hemorrhages and cerebrovascular accidents. The PRR for this HLT was calculated cumulatively from 1973 to 2013 and is shown in **Table 6-3** along with the PRR from the earlier interval. No signal was indicated from these data.

Table 6-3: Roche PRR for CNS haemorrhages and cerebrovascular accidents

Event	1973 - 2004	1973 - 2013
CNS haemorrhages and cerebrovascular accidents (HLT)	0.16	0.27

6.2.3 Bayer Safety Database ICSRs of CNS Hemorrhages and CVAs from 2001 to 2004

The estimated exposure to OTC oral naproxen sodium from April 1, 2001 to December 21, 2004 is 550,000,000 courses of therapy. A course of therapy is defined as two tablets per day for 10 days.

During this interval, a total of 29 case reports were retrieved from the Bayer PV database using the HLT Central nervous system haemorrhages and cerebrovascular accidents. The PRR for this HLT was calculated for all oral naproxen sodium formulations and is presented in **Table 6-4**. No signal was identified from these data.

6.2.4 Bayer Safety Database ICSRs of CNS Hemorrhages and CVAs from 2005 to 2013

The estimated exposures to oral naproxen sodium are based on sales data as presented in Bayer periodic safety update reports (PSURs). For the period of December 22, 2004 to August 1, 2013, the total estimated exposure to oral naproxen sodium was 1,334,000,000 courses of therapy. A course of therapy is defined as two tablets per day for 10 days.

During this interval, a total of 109 case reports were retrieved from the Bayer PV database using the HLT Central nervous system haemorrhages and cerebrovascular accidents. The PRR was calculated and is shown in Table 4 along with the PRR from the previous interval. No signal was identified from these data.

Table 6-4: Bayer PRR for CNS haemorrhages and cerebrovascular accidents

Event	1973 - 2004	2005 - 2013
CNS haemorrhages and cerebrovascular accidents (HLT)	0.24	0.17

6.3 Discussion and Summary of Postmarketing Case Reports of MIs and CVAs

In the Bayer data, the PRR for the HLT Ischaemic coronary artery disorders was calculated to be 0.38 for the period from 1994 to 21-Dec-2004. From 22-Dec-2004 to 01-Aug-2013, this PRR was found to be minimally elevated 1.02.

An examination of the database revealed that this increase is largely due to an increase in reporting of two specific PTs (Chest pain and Chest discomfort) within this HLT. Chest pain/discomfort are very nonspecific symptoms that could indicate a variety of conditions and do not necessarily indicate pain of a cardiac origin, however. In fact, the lack of a signal for acute MI/ MI is supported by the PRR < 1 for these events, both in the period up to 21-Dec-2004 (0.24) and from 22-Dec-2004 to 01-Aug-2013 (0.34).

Both the Roche and Bayer pharmacovigilance worldwide safety databases contained relatively few ICSRs of either myocardial infarction or cerebrovascular accident relative to the estimated extensive exposure to oral naproxen. This was true for the absolute number of ICSRs reported for both reporting periods.

In a parallel fashion, the PRRs for both periods and cumulatively for all terms examined were found to be low.

Therefore, based on the PRR methodology neither the Roche nor the Bayer spontaneously reported data indicate a signal for either myocardial infarction or cerebrovascular accident, for all periods examined.

7. Interaction with Aspirin

7.1 Background

Aspirin taken at low doses (81-325 mg daily) has been used for its cardioprotective antiplatelet effects.[j] In 2006, the Food and Drug Administration issued a notification to healthcare professionals about the interaction of ibuprofen with low dose aspirin (81 mg per day).[k] The combination may reduce the antiplatelet effect of aspirin, which may diminish its cardioprotective effect. It is uncertain if the interaction seen with ibuprofen also applies to naproxen or other NSAIDs. Naproxen has also been shown to inhibit human platelet aggregation in vitro by blocking the formation of thromboxane A2 (TXA2) [and consequently formation of its inactive metabolite, thromboxane B2 (TXB2)] via inhibition of COX-1 and the formation of PGI2, which is mostly COX-2 dependent.[6,54]

7.2 Mechanism of NSAIDs interaction with aspirin

It is thought that the interaction occurs through competitive inhibition by non-selective NSAIDs of the acetylation site of the COX enzyme in platelets. This competitive inhibition interferes with aspirin-mediated irreversible inhibition TXA2 production and subsequent platelet aggregation. The hypothesis is that when the non-selective NSAID is taken prior to aspirin, it will occupy the cyclooxygenase catalytic site, blocking the irreversible activity of aspirin required at the same site. This scenario will only allow for an incomplete and relatively brief inhibition of thromboxane and platelet anti-aggregation by the non-selective NSAID.

7.3 Clinical pharmacology studies reporting interaction of naproxen with aspirin

Several studies have looked at the potential interaction with naproxen and aspirin with respect to the outcome of platelet inhibition.

At high daily doses, concomitant use of naproxen did not result in an interruption of the antiplatelet benefits expected during aspirin therapy.[55] However, data from studies of lower doses may suggest that there is greater variability in degree and duration of thromboxane inhibition and that lower OTC doses that are not taken persistently may result in brief exposure to periods of modest elevations in thromboxane.

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[j] Aspirin's cardioprotective effects involve the prevention of cardiovascular (CV) thrombotic events in patients with or those at risk for cardiovascular disease (CVD). Specifically, the CV prevention indications for aspirin are, "To reduce the risk of death and nonfatal stroke with previous ischemic stroke or transient ischemia of the brain. To reduce risk of vascular mortality with suspected acute myocardial infarction (MI). To reduce risk of death and nonfatal MI with previous MI or unstable angina. To reduce risk of MI and sudden death in chronic stable angina pectoris. For patients who have undergone revascularization procedures with a preexisting condition for which aspirin is indicated."

[k] The FDA Postmarketing Drug Safety Information was published online in September 2006, available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125222.htm

Oldenhof *et al.* (2010) provides insight into the impact of thromboxane when low-dose aspirin and naproxen are taken concomitantly and when naproxen treatment is stopped.[56] With respect to the concomitant use of low-dose aspirin and naproxen, this study supports the conclusion that the significant thromboxane inhibition is maintained when naproxen is taken concomitantly with low-dose aspirin. These results are consistent with the findings from Capone 2005.[55] In both studies, when naproxen was administered concomitantly with low–dose aspirin, thromboxane inhibition was similar to aspirin alone and at a level considered sufficient to inhibit platelet aggregation. The data from Oldenhof (2010) and Capone (2005) studies support the conclusion that during concomitant use of low-dose aspirin and naproxen sodium at prescription (500 mg twice daily) and OTC (220 mg three times daily) doses thromboxane levels are significantly inhibited, similar to the level of thromboxane inhibition with aspirin alone.

Anzellotti *et al.* (2011) performed a cross-over, open-label study, in 9 healthy volunteers.[57] They received for 6 days 3 different treatments separated by 14 days of washout: i) naproxen 2h before aspirin; ii) aspirin 2h before naproxen; iii) aspirin alone. Naproxen given 2 hours before aspirin resulted in a 98% (90.6% to 99.44%) inhibition of serum thromboxane B2, 24 hours after administration on day 6 of treatment (primary endpoint). On day 6, at 24h after last dosing in volunteers on aspirin alone or aspirin given before naproxen, serum TXB2 was almost completely inhibited [99.1% (97.4%-99.4%) and 99.1% (98.0%-99.7%), respectively, median (range)]. Naproxen given before aspirin caused a slightly lower inhibition of serum TXB2 than the other 2 treatment schedules ($p=0.0007$ and 0.0045, respectively). All treatments produced a maximal inhibition of arachadonic acid (AA)-induced platelet aggregation. The authors concluded that sequential administration of naproxen 220 mg/BID and low-dose aspirin interferes with the irreversible inhibition of platelet COX-1 afforded by aspirin. The interaction was smaller when giving naproxen 2h after aspirin.

Two small RCTs have evaluated the effects of naproxen co-administered with aspirin on platelet inhibition.[58,59] Galliard-Grigioni *et al.* (2009) studied the influence of a co-administration of aspirin and NSAID on platelet aggregation in healthy subjects (n=11).[58] In a randomized, placebo controlled trial, naproxen was shown to enhance the platelet anti-aggregate action of aspirin after 24 h (closure time rising from 104±16 seconds at baseline to 212±69 seconds at 24 h, $p<0.001$), which was not seen with any other drug combination tested. This effect is lost after 4 days, suggesting that a regular daily co-administration of NSAID does not have an influence on platelet inhibition by aspirin.

Angiolillo *et al.* (2011) performed a Phase 1, single-center, double-blind, placebo-controlled study in health volunteers (n=40) aged 50-70 years to evaluate the impact of naproxen (500 mg twice daily) co-administered with low-dose, enteric-coated aspirin on COX-1 inhibition.[59] Patients received enteric-coated, low-dose aspirin (81 mg once daily) on days 1-5 (open-label period), then continue to receive the aspirin treatment and randomized for treatment with either naproxen plus esomeprazole magnesium or placebo twice daily on days 6-10 (randomized period). Angiollilo *et al.* (2011) found that low-dose aspirin co-administered with naproxen/esomeprazole magnesium is noninferior to aspirin use alone for platelet COX-1 inhibition. Specifically, serum TXB2 inhibition at measured at day 11 was 99.6% (90% CI: 99.4%-99.8%) in the naproxen/esomeprazole magnesium plus aspirin group versus 99.1% (90% CI: 98.7%-99.6%) in the placebo plus aspirin group. Similarly, the serum TXB2 inhibition was relatively unchanged at day 11 compared to day 6 baseline [naproxen/esomeprazole magnesium + aspirin: 99.2% (90% CI: 98.8%-99.6%); placebo + aspirin: 98.8% (90% CI: 98.2%-99.3%)].

7.4 Observational studies reporting data on the risk of cardiovascular events during concomitant use of NSAIDs (naproxen) and aspirin

Since 2005, two observational studies included a naproxen-aspirin cohort or subgroup.[60,61] Each compared the rates or odds of myocardial infarction events. Both studies reported no significant difference in rates of myocardial infarction in patients using naproxen with low-dose aspirin.

7.5 Summary of Interaction with Aspirin

The current evidence indicates some pharmacologic interaction between naproxen and the activity of aspirin. There is no evidence that occasional use of OTC doses of naproxen given with aspirin interferes with aspirin's cardioprotective effect. Specifically, co-administration of OTC naproxen (220mg TID) or prescription naproxen (550 mg BID) with low-dose aspirin allows platelet inhibition at equivalent levels as seen with low-dose aspirin alone. There is likely to be minimal risk from any attenuation of the antiplatelet effect of low dose aspirin with occasional use of naproxen.

8. Overall Conclusions

Naproxen is a dual COX-1/COX-2 inhibitor marketed in the US for both prescription and OTC use. Naproxen is known to inhibit platelet aggregation through its effects on COX-1 and thus, could potentially decrease the risk of cardiovascular events.

Naproxen has a well-documented CV safety profile, based on clinical study and worldwide patient use for over 38 years of prescription and OTC use. Naproxen has been used by millions of people as a safe and effective pain reliever.

In 2005, a review of clinical and observational studies, as well as postmarketing safety database analyses did not indicate any evidence of a safety signal for increased cardiovascular or cerebrovascular events during naproxen use. However, as part of a drug class labeling change requested by the US FDA, both the prescription and OTC naproxen labels were revised in 2005 to include more specific warnings regarding potential CV risk during NSAID use.

FDA is convening an Advisory Committee to review the CV safety of NSAIDs, including naproxen, since 2005 and to determine if additional changes in labeling would be required. We understand the rationale behind the use of NSAID class labeling. However, the body of evidence presented at the 2005 Advisory Committee meeting and new information published since 2005 demonstrates little to no association of an increased CV risk with naproxen. The benefit/risk for prescription and OTC naproxen remains unchanged.

As such, we believe that guidelines, publications and possibly the labeling should communicate the low CV risk for naproxen, particularly for Aleve® in its OTC setting. Data consistently demonstrate that naproxen has a lower overall CV risk than other selective and non-selective non-aspirin NSAIDs.

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Appendix 1 Current OTC Label

Aleve® Tablets

Drug Facts

Active ingredient (in each tablet) ***Purposes***

Naproxen sodium 220 mg (naproxen 200 mg)
(NSAID)*.....Pain reliever/fever reducer

*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
  - minor pain of arthritis
  - muscular aches
  - backache
  - menstrual cramps
  - headache
  - toothache
  - the common cold
- temporarily reduces fever

Warnings

Allergy alert: Naproxen sodium may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you:

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs (aspirin, ibuprofen, naproxen, or others)
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if

- the stomach bleeding warning applies to you
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, or kidney disease
- you are taking a diuretic
- you have problems or serious side effects from taking pain relievers or fever reducers
- you have asthma

Ask a doctor or pharmacist before use if you are

- under a doctor's care for any serious condition
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

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Aleve® Tablets

Stop use and ask a doctor if

- you experience any of the following signs of stomach bleeding:
  - feel faint
  - vomit blood
  - have bloody or black stools
  - have stomach pain that does not get better
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- you have difficulty swallowing
- it feels like the pill is stuck in your throat
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use naproxen sodium during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- drink a full glass of water with each dose

Adults and children 12 years and older	• take 1 tablet every 8 to 12 hours while symptoms last • for the first dose you may take 2 tablets within the first hour • do not exceed 2 tablets in any 8- to 12-hour period • do not exceed 3 tablets in a 24-hour period
Children under 12 years	• ask a doctor

Other information

- **each tablet contains:** sodium 20 mg
- store at 20-25ºC (68-77ºF). Avoid high humidity and excessive heat above 40°C (104°F).

Inactive ingredients FD&C blue #2 lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, titanium dioxide

Questions or comments? **1-800-395-0689** (Mon – Fri 9AM – 5PM EST) or www.aleve.com

Bayer HealthCare
Consumer Care Division

Appendix 2 OTC Label Prior to 2005

Aleve Tablets

Drug Facts

Active ingredient (in each tablet) ***Purposes***
Naproxen sodium 220 mg (naproxen 200 mg)....Pain reliever/fever reducer

Uses
- temporarily relieves minor aches and pains due to:
  - minor pain of arthritis
  - muscular aches
  - backache
  - menstrual cramps
  - headache
  - toothache
  - the common cold
- temporarily reduces fever

Warnings
Allergy alert: Naproxen sodium may cause a severe allergic reaction which may include:
- hives
- facial swelling
- asthma (wheezing)
- shock

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take naproxen sodium or other pain relievers/fever reducers. Naproxen sodium may cause stomach bleeding.

Do not use if you have ever had an allergic reaction to any other pain reliever/fever reducer

Ask a doctor before use if you have ever had serious side effects from any pain reliever/fever reducer

Ask a doctor or pharmacist before use if you are
- under a doctor's care for any serious condition
- taking any other drug
- taking any other product that contains naproxen sodium, or any other pain reliever/fever reducer

Stop use and ask a doctor if
- an allergic reaction occurs. Seek medical help right away.
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- you have difficulty swallowing
- it feels like the pill is stuck in your throat
- you develop heartburn
- stomach pain occurs or lasts, even if symptoms are mild
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use naproxen sodium during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- **do not take more than directed**
- drink a full glass of water with each dose

Adults and children 12 years and older	• take 1 tablet every 8 to 12 hours while symptoms last • for the first dose you may take 2 tablets within the first hour • the smallest effective dose should be used • do not exceed 2 tablets in any 8- to 12-hour period • do not exceed 3 tablets in a 24-hour period
Adults over 65 years	• do not take more than 1 tablet every 12 hours unless directed by a doctor
Children under 12 years	• ask a doctor

Aleve Tablets

Other information
- **each tablet contains:** sodium 20 mg
- store at 20-25ºC (68-77ºF). Avoid high humidity and excessive heat above 40°C (104°F).

Inactive ingredients FD&C blue #2 lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, titanium dioxide

Questions or comments? **1-800-395-0689** or www.aleve.com